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A SEQUENTIAL EVALUATION OF LEFT VENTRICULAR FUNCTION IN ASYMPTOMATIC AND SYMPTOMATIC PATIENTS WITH CHRONIC SEVERE AORTIC REGURGITATION

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ABSTRACT OF THESIS:

The optimal timing of valve replacement surgery in chronic severe aortic regurgitation (AR) has remained a major clinical problem in the management of these patients. Although the onset of symptoms is the generally accepted indication for aortic valve replacement (AVR), the unpredictable development of pre-symptomatic left ventricular (LV) dysfunction as a result of prolonged volume overload has resulted in numerous reports attempting to formulate a risk profile for these patients. Although aortic root and LV cineangiography have been the "gold standard" for defining the severity of AR and its effect on LV performance, serial follow-up by these means is impractical. More recently numerous non-invasive measures of LV size (echocardiogram) and function both at rest and on exercise (echocardiogram and equilibrium radionuclide angiocardiography, ERNA) have been serially utilised. In these endeavours, the thinking has been clouded by a tendency to equate these two measures and failing to appreciate that apparent pre-operative LV dysfunction (particularly on exercise) may be rapidly reversible by AVR and the consequent changes in LV loading conditions.

This study was a prospective, sequential evaluation of left ventricular function using both non-invasive and invasive techniques in symptomatic and asymptomatic patients with isolated chronic, severe (4+) AR at cardiac catheterisation. The aims of the study were to (I) Identify differences in the clinical, echocardiographic, resting and exercise haemodynamic and radionuclide measures of left ventricular function in symptomatic and asymptomatic patients with chronic severe A.R. with particular

reference to the incidence of presymptomatic development of left ventricular dysfunction. (II) Critically evaluate the role of exercise stress (both isotonic and isometric) in the assessment of patients with chronic severe A.R. (III) Evaluate the influence of time (sequential studies) on the haemodynamic burden in asymptomatic patients. (IV) Study the impact of successful aortic valve replacement on the reversibility of abnormal pre-operative LV function in an attempt to predict which patients would benefit from this therapeutic intervention and whether operation for symptoms alone is the correct clinical practice.

Thirty two (32) symptomatic patients and twenty eight (28) asymptomatic patients with chronic severe AR formed the patient cohort. The initial evaluation included an assessment of clinical status, echocardiographic LV dimensions and systolic function, resting and exercise ERNA with simultaneous haemodynamic monitoring, and cardiac catheterisation including coronary angiography. Two forms of exercise were used, namely graded, symptom-limited supine and erect bicycle exercise and isometric handgrip. Twenty two (22) of the symptomatic group underwent AVR and 19 patients were re-evaluated 6 months postoperatively. Twenty six patients (23 asymptomatic and 3 unoperated symptomatic patients) were sequentially evaluated at 6 months after the initial assessment, with 9 patients re-assessed at 12 months.

At the initial assessment, the clinical evaluation (including the degree of LV hypertrophy on the electrocardiogram and the cardio-thoracic ratio) and echocardiographic LV dimensions and systolic function did not help in the differentiation of symptomatic from

asymptomatic patients. The exercise study confirmed that a drop in LV ejection fraction (LVEF) on exercise is common, occurring in 81% of the symptomatic group and approximately 50% of the asymptomatic patients. Contrary to earlier reports, posture was not found to be important in the stratification of patients on the basis of LVEF response to exercise. Upright exercise more closely resembles normal daily activity and is recommended as the posture of choice in the exercise evaluaton of patients with chronic severe AR.

Resting LVEF did not appear predictive of this exercise response which occurred early during graded supine bicycle exercise. Low level exercise is thus adequate to stratify patients based on LV functional reserve, accepting the fact that a normal exercise capacity has been shown to be an independent prognostic factor. Exercise LVEF correlated poorly with other measured variables (haemodynamic and radionuclide). This finding is not surprising given the known limitations of this dimensionless measure of LV function.

Despite some of the theoretical advantages, it would appear that, isometric handgrip exercise is not a satisfactory alternative to dynamic exercise.

A decrease in LV dilatation following AVR is confirmed but occurred later (between 2 weeks and 6 months)than in many earlier reports. However, patients with marked pre-operative LV dilatation ran a major risk of persistent postoperative LV enlargement. The prognostic value of a pre-operative end-systolic dimension (DES) of > 55mm was not substantiated but the sample size was small. In addition, my study confirmed that regression of left ventricular

hypertrophy (LVH) is a slow process following aortic valve replacement.

Although the sequential assessment showed a gradation to abnormality in some of the haemodynamic measures and a progressive increase in the number of patients with an abnormal LV functional reserve, it is important to note that some patients showed a variable LVEF response to exercise on repeat testing.

The most important findings were in the postoperative evaluation and serve to confirm our present practice at this institution of only recommending AVR in symptomatic patients with chronic severe aortic regurgitation.

These included a marked improvement in symptomatic status, a normalisation or near-normalisation of LV mass, diastolic filling patterns and resting and exercise LVEF in approximately 75% of cases. These favourable changes could not be predicted from the level of pre-operative exercise LVEF and serve to confirm that an abnormal LV functional reserve is not of any prognostic significance.

Despite normalisation of the echocardiographic dimensions and resting LVEF, pulmonary capillary wedge pressure (PCWP) at rest remained abnormal in one third of the patients and was markedly elevated on exercise in the majority of the group (87.5%). These observations cannot be adequately explained by persistent LV hypertrophy or abnormal diastolic filling and may reflect the preload dependance of this chronically volume overloaded left ventricle.

In conclusion, it would appear reasonable to delay aortic valve replacement in chronic severe aortic regurgitation until the development of symptoms, negating the need for sophisticated, expensive and time-consuming follow-up. This is particularly relevant in our society where resources are limited and patients often present late in the natural history of this disease.

DEDICATION:

For Ghita, Craig and Kerri

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STATEMENT OF CANDIDATE

I declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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CHAPTER I

HISTORICAL REVIEW

Although Sir Dominic Corrigan (Corrigan 1832) published the classic monograph on aortic regurgitation in 1832 entitled "On Permanent Patency of the Mouth of the Aorta or Inadequacy of the Aortic Valves", earlier reports on the pathology and clinical manifestations date back to the early seventeenth century. These have been eloquently cited by Crawford Adams (Adams 1969).

In 1615 Helkiah Crooke (Crooke 1615) described the pathologic findings of aortic regurgitation associated with dilatation of the heart: "In the dilatation of the heart they (aortic cups) are all extended, the forked valves making certain gaping fissures between their forkes, by which the matters are let in".

Raymond de Vieussens in 1695 described the clinical manifestations of aortic insufficiency published in his book Novum Vasorum Corporis Humani Systema(Vieussens 1705) and in 1715 (Vieussens 1715) described the pulse of aortic insuficiency as "..... very full, very fast, hard and unequal and so strong the arteries on both sides struck the fingers like a tense cord vibrating violently". William Cowper (Cowper 1703 - 1712) in 1705 described the pathophysiologic basis of symptoms due to volume and pressure overload of the left ventricle in his paper, "Of Ossifications or Petrifactions in the Coats of Arteries, Particularly in the Valves of the Great Artery."

"The explication of the symptoms in both these cases is obvious enough; for though the person in the first instance did not die of

the same disease as the other, yet the symptoms in his illness plainly showed what must follow from the disorders of these valves, as they are rendered more or less useless; for as their office is to prevent the return of the blood into the heart, in its diastole, by exactly shutting up the passage of the aorta, like the valves in water engines, so if by an accident they are hindered from doing their duty, as they were by the petrifications mentioned, the consequences must be, not only a regurgitation of blood into the heart. In the latter instance, these valves were wholly useless, and the circulation became more difficult, as appeared by the refrigeration of the extreme parts. - In both cases, the left ventricle of the heart was dilated proportionately to the bad constitution of these valves, which plainly shows these valves give such assistance to the heart, as it cannot be without, and that it gradually suffers according to their indisposition".

The haemodynamic characteristics were further amplified in 1761 by John Baptist Morgagni (Morgagni 1761) in his "Letter the Twenty-third, Article 9":-

".....; so that, as some portion of it returned into the left ventricle of the heart, when this ventricle ought to receive the blood that was coming in from the lungs, it would necessarily happen, that the returning portion, as well as the portion which had not been extruded just before, must occupy some part of that space, which, from the design of nature, was entirely due to the blood that was coming in from the lungs. Which circumstance, finally, could not but overload both the lungs and the heart, and compel the latter to throw out, every now and then, with a great impetus, the blood that stagnated in it".

Further knowledge of the signs of aortic insufficiency were described in 1827 by Thomas Hodgkin in a paper read before the Hunterian Society and later published in the Medical Gazette(1871) and described in Wilks' historical note on Valvular Disease of the Heart. He refers to the great enlargement of the heart that ensues, and of the "bruit de scie" heard during life owing to the blood being subjected to two motions, the one progressive, the other retrograde. He describes the case of a friend Dr Cos, a travelling physician to Sir R K Porter who was an active sportsman despite severe aortic regurgitation. He exhibited the heart to the Society, which was much enlarged, and one valve was elongated and hung down towards the ventricle (Specimen now in Guy's Hospital Museum, No. 1427). In the 1829 Lumleyan Lectures before the Royal College of Physicians, John Elliotson described a bellows-murmur due to aortic regurgitation. This lecture was published in 1830.

James Hope took exception to Corrigan's initial claim and emphasised that aortic regurgitation was first described in his treatise on Diseases of the Heart published in December 1831. However, he corrected this impression in the 1842 first American edition of Diseases of the Heart(Hope 1842) and gave credit to John Elliotson. In his treatise he describes the quality and location of the murmur, points out that it is of very frequent occurrence, though commonly supposed to be rare and that the reason for this was that it was invariably mistaken for a murmur from the mitral valve.

In Corrigan's classic monograph, "On Permanent Patency of the Mouth of the Aorta or Inadequacy of the Aortic Valves" published in 1832 in the Edinburgh Medical and Surgical Journal, he makes three

pertinent and interesting observations:-

Figure 1.1 CORRIGAN'S ORIGINAL PUBLICATION

ON PERMANENT PATENCY OF THE MOUTH OF THE AORTA, OR INADEQUACY OF THE AORTIC VALVES*

By

D. J. CORRIGAN, M.D.

One of the physicians to the Charitable Infirmary, Jervis Street, Dublin; Lecturer on the Theory and Practice of Medicine; Consulting Physician to St. Patrick's College, Maynooth

(i) Firstly, he appreciated the varied pathological conditions which may affect the valve , ".... morbid affection of the valves and aorta permitting this regurgitation are - that the valves may be absorbed in patches, - reticulated and present holes; may be ruptured, - flapping back into the ventricle; - may be tightened or curled in against the sides of the aorta; - or without any proper organic lesion may be rendered inadequate to their function by dilatation of the mouth of the aorta, - and the blood then, as in the other instances, regurgitates freely into the ventricle."

(ii) Secondly, he recognised that symptoms are non-specific but appreciated the diagnostic importance of the physical signs and gives a detailed description of the pathophysiologic mechanisms behind these signs - ".... what is deficient in general symptoms from their obscurity is, however, amply supplied by the certainty of the physical and stethoscopic signs, which may be referred to the three following indications:-

(a) Visible pulsation of the arteries of the head and superior extremities.

(b) "Bruit de soufflet" in the ascending aorta, in the carotids, and subclavians.

(c) "Bruit de soufflet" and "fremissemont" or a peculiar rushing thrill felt by the finger, in the carotids and subclavians. In conjunction with these may be reckoned the pulse, which is invariable full."

(iii) Thirdly, he astutely appreciated and reported the fact that chronic severe aortic regurgitation is characterised by a protracted clinical course - "Although the cure of Inadequacy of the Aortic Valves is probably out of the reach of medicine, a correct knowledge of the nature of the affection is not the less necessary. The patient is relieved from harassing treatment, that, however applicable in other cases of heart disease, is not alone useless, but positively injurious in this. In other affections of the heart there is constant danger of sudden death from pulmonary apoplexy or haemorrhage, which may be induced even by ordinary exertion, and such danger keeps the patients in a state of perpetual terror. In this disease, on the contrary, assurance may be given against any sudden termination; and the patient may be permitted not only to attend to his business or profession, but may be assured, that in leading a life of business and tolerable activity, he is adopting the very best means to prolong his life. Under treatment such as recommended, it is astonishing what little uneasiness inadequacy of the aortic valves will produce".

This appreciation is the dilemma of the practising cardiologist today. Now that treatment for aortic regurgitation is available the decision as to when to intervene is difficult and forms the basis of the thesis.

Although the presence of a double murmur heard by pressure of the stethoscope was first described by Bouilland, its importance was emphasised by his pupil Paul Louis De Roziez in his paper on "The Double Intermittent Murmur over the Femoral Arteries as a sign of Aortic Insufficiency" published in 1861. This murmur later became known as "DuRoziez's sign". In this report he makes a number of important points, viz:-

(i) The double intermittent murmur described by many authors was never given as a constant sign in this lesion.

(ii) Most commonly it is not present and it is necessary to produce it by compression - the finger, compressing the artery about two centimeters above the stethoscope, produces the first murmur; two centimeters below, the second murmur.

In subsequent years clinical observation has made it increasingly evident that, while DuRoziez's sign usually can be elicited in patients with the intracardiac signs of aortic regurgitation, these phenomena are not mutually dependent - one may be present without the other. The diagnostic significance of DuRoziez's sign consequently has occasioned considerable discussion and investigation.

A few years later Traube (Traube 1872) described a double tone (Doppeltone) which could be heard in rare cases by applying the stethoscope lightly over the femoral artery, so that the diameter of the vessel was not modified by the compression. The fundamental work of DuRoziez and Traube made many points clear concerning the causation of these murmurs and sounds despite the confusion introduced by later workers. The first arterial murmur was explained as caused by the eddies which are formed by the pulse wave under the narrow arterial section where the stethoscope is applied. The second murmur was explained as caused by a backward wave coming from the periphery and the centripetal nature of the wave was admitted by all later authors.

The presystolic murmur which sometimes accompanies aortic regurgitation, later to be known as the Austin Flint murmur, was first observed in 1859 by Dr A Flint in examining a patient with well-marked signs of aortic regurgitation in whom a presystolic murmur was audible at the apex. At autopsy however, the mitral valve was found to be normal. This classic desription was published in 1862 in the American Journal of the Medical Sciences(Flint 1862). Flint heartily disapproved of associating any physical sign with the name of the original describer and wrote (Landis 1912): "So long as signs are determined from fancied analogies, and named from these or after the person who describes them, there cannot but be obscurity and confusion."

From the time of these early descriptions, the medical treatment of aortic regurgitation of severe degree had been unsatisfactory. Although it was appreciated that the asymptomatic state may be present for many years, the onset of symptoms heralded a rapid

downhill course (Langley 1921, Reader 1947 and Webster 1953). In general however, the prognosis was better in the rheumatic group than the syphilitic group. Signs of poor prognosis included severe praecordial pain, severe congestive heart failure, cardiomegaly, low diastolic pressure, prolongation of the PR interval and active endocarditis.

Once surgery became possible for the management of severe aortic regurgitation, with Hufnagel in the 1950s (Hufnagel 1954) and later Starr(Starr 1963) in 1960 using a ball valve prosthesis and Ross (Ross 1966)and Barratt-Boyes (Barratt-Boyes 1965) inserting the first homografts a few years later, it became particularly important to know about the natural clinical course of this condition, so as to more optimally select patients for valve replacement surgery. In 1956 Segal, Proctor Harvey and Hufnagel (Segal 1956) reported their experience with a selected population of 100 cases of severe aortic regurgitation referred to the Georgetown University Medical Centre for cardiac evaluation and suitability for insertion of the Hufnagel aortic plastic valve. Although many interesting and unusual clinical features became evident from this study, they were able to particularly emphasise the natural history of chronic rheumatic aortic regurgitation. The following profile history typified the average patient with aortic regurgitation: acute rheumatic fever at the age of 13 years with recurrent attacks in subsequent years; haemodynamically significant aortic regurgitation by age 20 years; a ten year "asymptomatic" period, followed by the final phase of 6.4 years from the onset of symptoms to the time of evaluation. Usually the symptoms were slowly progressive in nature, first manifested by mild dyspnoea on effort or a sensation of increased cardiac thrust. They emphasised

the frequency of classic angina (almost 50% of cases), occurring in the majority a few years after the onset of dyspnoea on effort. The average age of those with and without angina was the same.

The symptom was usually effort induced but rest angina did occur fairly commonly - autopsies in a number of these cases showed no evidence of coronary artery disease or ostial narrowing. They proposed three pathophysiological mechanisms namely:-

(i) Marked lowering of diastolic pressure with resultant decrease in coronary blood flow,

(ii) The "sucking" action of the regurgitant stream on the coronary arteries (Bernouilli's principle),

(iii) Relative coronary insufficiency related to the large left ventricular mass.

They were able to show that the following clinical and radiographic factors indicated a poor prognosis:-

(i) Recent occurrence of bacterial endocarditis with subsequent increasing signs of aortic regurgitation

(ii) Co-existence of angina and congestive heart failure

(iii) Syphilitic aetiology

(iv) Marked cardiomegaly

(v) Increasing age (over 40 years)

(vi) Increasing duration of symptoms.

In addition, approximately 5% of these patients with severe, fairly well compensated, aortic regurgitation died suddenly and unexpectedly. Ventricular premature beats were common in this group and the presumed mechanism of death was ventricular fibrillation. Neither this group nor patients who died soon after

their episode of heart failure were included in this evaluation.

In subsequent studies to refine patient selection for surgery:-

(1) Spagnuolo et al (Spagnuolo 1971), in evaluating the medical course of 174 patients with rheumatic aortic regurgitation prospectively followed for a median of 10 years, were able to show by life table analysis that the development of the triad of moderate or marked left ventricular enlargement on chest X-ray, left ventricular hypertrophy with or without repolarisation change on electrocardiogram and an abnormal blood pressure (systolic BP > 140, diastolic BP <40) were the criteria predictive of death, congestive heart failure and angina. By one year, a third of patients in the "high risk" group had reached one of his end-points, increasing progressively until by 6 years only 13% of patients had not died or had an episode of congestive heart failure or angina. This study included most of the patients at risk, and took into account year-by-year changes in clinical status. The deterioration was particularly rapid within the first 3 years from the fulfillment of the "high risk" criteria.

(2) Goldschlager et al (Goldschlager 1973), in a combined prospective and retrospective analysis of clinical and haemodynamic data in 150 patients with aortic regurgitation of varying aetiologies, confirmed the protracted clinical course of chronic aortic regurgitation. They also highlighted the still unresolved dilemma of the late appearance of clinical disability at a stage when irreversible myocardial damage may have occurred. However, with a ten year prosthetic valve attrition rate of 25-50%, as well as numerous non-fatal

complications, they cautioned that both early operation and prolonged procrastination appeared to be equally unsatisfactory approaches to patients with chronic severe aortic regurgitation. In reporting the rest and exercise haemodynamic profiles in their patients, in accordance with the earlier work of Lewis (Lewis 1970), they found them normal in 50% of cases at rest and in one-third of all cases after 4 minutes of supine bicycle exercise. The earliest abnormality was an elevation of left ventricular end-diastolic pressure (measured by pulmonary capillary wedge pressure) occurring initially as an isolated abnormality during exercise. This they presumed to be due to decreased compliance of the hypertrophied left ventricle. Ross et al (Ross 1971) showed that chronic volume overload in dogs resulted in a dilated left ventricle with a steep pressure - volume relationship and therefore a less compliant chamber. Additional factors are the inevitable intramyocardial fibrosis associated with severe left ventricular hypertrophy and the altered ventricular geometry and ultrastructure (Meesner 1968, Fanburg 1970). Clinical disability developed when there was a more pronounced haemodynamic abnormality, namely a combination of elevated filling pressure and reduced flow (cardiac output) at rest.

(3) Rapaport (1975) at a Symposium on the Effect of Surgical Treatment on the Natural History of Acquired Heart Disease, presented the survival statistics for patients seen at the University of California Medical Centre in San Fransisco. He stated that moderate or severe aortic regurgitation had a relatively good prognosis with a 10 year survival rate of about 50%. He also reported that serious cardiovascular

symptoms occurred relatively late in the course of the disease, but once cardiac decompensation supervened, the patients condition usually deteriorated rapidly. Most patients died within 2 years of the onset of congestive heart failure and within approximately 5 years of the onset of angina. These results were in agreement with other reports (Massell 1966, Dexter 1969).

(4) Smith et al (Smith 1976) from Green Lane Hospital, Auckland, New Zealand, investigated the indications for surgical intervention in the treatment of severe rheumatic aortic regurgitation. In evaluating 180 patients between 1957 through 1967, using 39 clinical and haemodynamic parameters in an attempt to define those associated with increased pre-operative death, higher operation mortality and morbidity and poor long term survival, only 3 proved to be reliable indicators for operative intervention. These included:-

(i) Cardio-thoracic ratio greater than 0.60

(ii) A history of heart failure, and

(iii) Extreme left ventricular hypertrophy on electro-cardiogram.

No factor predisposed to surgical complications and although surgery could be safely postponed until these above criteria were met, premature ventricular contractions and independent evidence of myocardial disease were further factors that were considered to influence the timing of operative intervention. In contrast to other studies (Bland 1957, De Georges 1966) citing the onset of angina as a poor prognostic feature, this series revealed that the presence of pre-operative angina

alone did not affect early or late survival results (all patients with angina who died pre-operatively had other unfavourable features). They postulated that, although the simpler clinical observations used in their study allowed a surprisingly accurate prediction of outcome, serial non-invasive measurements of myocardial function might improve the assessment of optimal timing of surgery. It is the evolution of these measures that I will review in Chapter II.

CHAPTER II

THE TIMING OF SURGERY IN SEVERE AORTIC REGURGITATION: - A REVIEW OF THE LITERATURE

II.0.0 INTRODUCTION

Over the past 25 years, valve replacment surgery has emerged as the most important advance for the management of patients with valvular heart disease(Rahimtoola 1983). The first diseased aortic and mitral valves were replaced with ball-valve prostheses in 1960 by Harken (Harken 1960) and Starr et al (Herr 1968, Starr 1971), followed by homograft devices a few years later for aortic valve replacement by Ross (Ross 1967) and Barratt-Boyes (Barratt-Boyes 1967).

This therapeutic option has both evolved and changed over the past 2 decades with superior results attributed to:-

(a) Improved operative techniques (McGoon 1967, Maloney 1974, Bigelow 1975, Chapin 1975, Baird 1975, Buckberg 1977, Kirklin 1979).

(b) Better prosthetic devices - although innumerable devices have been evaluated, the majority have not stood the test of time and the perfect valve substitute still has to be developed.

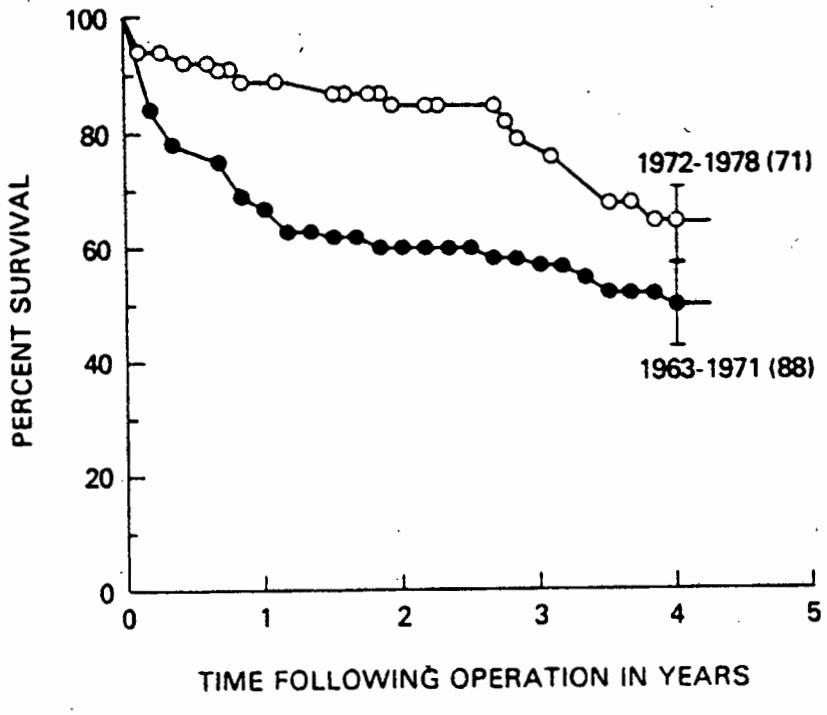
(c) Better peri- and post-operative management(Oldfield 1985).

(d) Possibly earlier surgery i.e. in the 1960's class III and IV NYHA patients formed the majority of the cohort, whereas more recently predominantly Class II with a smaller proportion of Class I and III patients have undergone aortic valve replacement (Pluth 1974, Carey 1974, Starr 1974, Bonchek 1975, Kouchoukos 1976).

Although symptomatic relief and subsequent improved quality of life are the main indications for valve replacement, when severe symptoms are used as the only indicator, long term postoperative results have been considered to be disappointing (Herr 1968, Beall 1969, Duvoisin 1969, Aston 1971, Rotman 1971, Shean 1971, Hirshfeld 1974, Isom 1974, Badenhorst 1975, Roberts 1976, Rubin 1977, Bonow 1982).

The following figure(Fig. 2.1) shows the survival after aortic valve replacement for consecutive symptomatic patients with aortic regurgitation at the National Institutes of Health from 1963 to 1971 and from 1972 to 1978. Numbers in parentheses indicate the number undergoing operation during each period:-

Figure 2.1 NIH SURVIVAL DATA FOLLOWING AVR(1963 to 1978)



(Figure 1, Am J Cardiol 50;326,1982)

In the years 1963 to 1971, during which period 88 patients underwent aortic valve replacement for severe symptomatic aortic regurgitation at the National Institutes of Health, the survival at 1 year was 60% with a 4 year survival of 50%. Although in the years 1972 to 1978 operative mortality (6%) and early (2 year) postoperative survival improved (85%), probably reflecting improved operative techniques (Pupello 1976, Adams 1978, Richardson 1979, Kirklin 1979), perioperative care (Pupello 1976, Copeland 1977, Rubin 1977, Cohn 1981) and valve design, the 4 year survival of 63% was only slightly better than the earlier period. Similar experiences were reported from many other centres (Copeland 1977, O'Toole 1978, Schwartz 1979, Clark 1980, Henry 1980, Cohn 1981, Greves 1981). Seventy eight percent of late postoperative deaths were due to congestive heart failure. It was postulated that prolonged volume overload of the left ventricle led to irreversible LV dysfunction and it was considered important to define pre-operative markers that would predict a high risk of dying from congestive heart failure secondary to left ventricular dysfunction during long term follow-up.

Another important consideration therefore, is the role of the valve replacement in the preservation of left ventricular function. Successful valve replacement has been shown to preserve left ventricular function and prolong life in patients with severe aortic regurgitation by preventing the late development of heart failure(Bonchek 1975, Kouchoukos 1976). As early as 1974, Starr (Starr 1974) and Carey et al (Carey 1974) proposed the role of early valve replacement in asymptomatic or minimally symptomatic patients, using the rationale of reduced operative mortality,

improved device design, clarification of long term results against the background of the known prognostic significance of pre-operative measures of left ventricular function and the recognition of congestive heart failure in causing late morbidity and mortality (Barnhorst 1975, Bonchek 1975, Bonow 1982). In contrast to this view however, clinicians are faced with:-

(i) the unpredictable postoperative functional result after aortic valve replacement.

(ii) the major problem of valve related morbidity and mortality.

(iii) the many problems associated with the analysis of published data.

(iv) the excellent prognosis with conservative, non-operative management in patients with severe aortic regurgitation and normal left ventricular function (vide infra).

A number of important factors therefore need consideration prior to the recommendation of early valve replacement for the preservation of left ventricular function, namely:-

1.0 Prosthetic heart valves and their problems.

2.0 The natural history of asymptomatic severe aortic regurgitation and normal left ventricular function.

3.0 The development of pre-symptomatic left ventricular dysfunction.

4.0 The non-invasive evaluation of left ventricular function in symptomatic patients with severe aortic regurgitation - echocardiographic and radionuclide markers of poor postoperative survival.

5.0 The non-invasive evaluation of left ventricular function in asymptomatic severe aortic regurgitation.

6.0 Postoperative assessment.

7.0 Problems associated with published data.

These aspects are addressed in more detail in this chapter.

II.1.0 PROSTHETIC HEART VALVES AND THEIR PROBLEMS:

An appreciation of the operative, perioperative and postoperative morbidity and mortality associated with prosthetic heart valves is fundamental to the management of patients with chronic aortic regurgitation. Although reports in the literature may serve as guidelines, the experience in one's own institution(Cardiac Clinic, Groote Schuur Hospital) should be the ultimate guide in the timing of operative intervention, always remembering that valve replacement is a palliative procedure, leaving the patient device-dependent (Rahimtoola 1980). Over the past five years(1981 to 1985) the operative mortality for aortic valve replacement(elective and emergency) at our hospital has ranged from 1.5% to 5.4% with a mean of 3.2%(unpublished data).

II.1.1 Operative Mortality:

The published data on the operative mortality rate for aortic valve replacement in the late 1970's from leading centres in the United States of America and elsewhere varies considerably, with quoted operative mortalities of between 3% and 12% (Karp 1974, Barnhorst 1975, Lee 1975, Bjork 1976, Daenen 1976, Barratt-Boyes 1977, Blackstone 1977, Copeland 1977, Ionescu 1977, Thompson 1977, Starr 1977, Cohn 1981). An estimate of 5-7% is reasonable. Factors contributing to a high operative mortality include heart failure, reduced left ventricular function, poor effort tolerance (New York Heart Association Class III or IV) and associated coronary artery

disease. Nevertheless the major cause of death is the low output state due to pre-existing or perioperative myocardial damage. This factor assumes critical importance in patients with severe aortic regurgitation where left ventricular mass may be two to three times normal (Pantely 1978). However, with better techniques of myocardial protection, namely the use of cold cardioplegia with potassium ion arrest and topical cooling, there has been a significant reduction in perioperative myocardial damage and operative mortality, with the long-term benefit still to be evaluated (Adams 1978, Conti 1978, Kirklin 1979, Richardson 1979). Currently, a reasonable estimate of perioperative myocardial damage is 5%.

II.1.2 Influence of Valve Replacement on Left Ventricular Functon: It is important to consider the intra-operative, perioperative and late postoperative periods, and although methods of myocardial protection have been refined, no adequately defined method of assessing postoperative myocardial damage has been reported. Electrocardiographic Q wave criteria, which usually underestimates myocardial damage (Klausner 1977, Righetti 1977, Ellis 1979), reveal a 10-12% peri-operative myocardial infarction rate in patients undergoing aortic valve replacement, predominantly in patients with associated coronary artery disease. However, myocardial infarction also occurs in patients without coronary artery disease, reported at approximately 5% (Murphy 1977, Oldfield 1985), and is presumably related to left ventricular hypertrophy and an inadequate supply of cardioplegia to the hypertrophied myocardium. Severe myocardial damage can also occur in the absence of pathological Q waves - in such cases myocardial infarction is

presumably non-transmural but may be extensive. In addition, varying degrees of reperfusion damage may contribute to the overall injury sustained by the left ventricle during surgery.

The late results are not accurately defined and at present are largely unknown, although Turina et al (Turina 1984) have shown a substantial improvement in late postoperative survival of patients with chronic aortic regurgitation during the past decade as a result of a reduction in the frequency of death caused by post-operative heart failure; this improvement is attributed to earlier operation. However, if patients remain free of complications and left ventricular dysfunction is not too far advanced, improved left ventricular function is the rule following aortic valve replacement (Gault 1970, Doces 1974, Dodge 1974, Bristow 1975, Morton 1976). This is in contrast to patients undergoing mitral valve replacement (Doces 1975). This hypothesis must be viewed with the background knowledge that there exists a major problem in evaluating the effects of valve replacement on ventricular function, namely, the difficulty in separating the effects of removal of abnormal loading conditions from those of primary myocardial dysfunction (Rahimtoola 1977).

II.1.3 Long Term Record of Prosthetic Devices:

Actuarial techniques (Cutler 1958) probably allow the most meaningful analysis of long term results, and require adequate numbers of patients with at least 5 years of follow-up and appropriately presented data to allow assessment of longterm complication rates, including durability, thrombogenicity and haemodynamic efficiency.

At present the intermediate and longterm results are only known for some of the mechanical prostheses (LeFrak 1979, Teply 1981, McGoon 1984), and although the initial results with bioprostheses appeared encouraging with estimated survival times of 12-15 years and the advantage of patients in sinus rhythm not requiring anticoagulation (Hannah 1975, Angell 1977, Ionescu 1977, Stinson 1977), it is important to appreciate that an incidence of thromboembolism of up to 2% has been reported in the literature (Stinson 1977, Cohn 1979). In addition, premature failure due to valve degeneration occurring less than 4 years after valve replacement is well recognised particularly in young patients. This is of particular importance in the South African context where many of our patients coming to valve replacement are <35 years old(Rose 1978, Thandroyen 1980, Curcio 1981). The status of patients 10 years after aortic valve replacement, derived from numerous publications, with some extrapolation of data and appreciating that improved device design and operative techniques may lower the incidence of some complications, can be summarised in the Table 2.1 (Bjork 1979).

Table 2.1 STATUS OF PATIENTS 10 YEARS AFTER AORTIC VALVE REPLACEMENT:

Status	Percent
Dead	40-60
Perioperative myocardial infarction	>5
Reoperation	10-20
Thromboembolism	10-20
Major hemorrhage with anticoagulants	10-15
Minor hemorrhage with anticoagulants	20-30
Prosthetic endocarditis	10

(Table III, J Thorac Cardiovasc Surg 79;164,1980)

Two recent 10-20 year follow-up studies have been published and deserve more detailed review. The first is a 20 year follow-up study on patients operated on from 1960 to 1980 by Teply and Starr et al (Teply 1981) using the Starr-Edwards caged-ball valve prosthesis. The 10 and 15 year survival for isolated aortic and mitral valve replacement was similar; 56% at 10 years and 44% at 15 years, with a lower survival rate for patients undergoing multiple valve replacement. By multivariate analysis, the year of operation was the most important determinant of late survival with a 5 year survival of patients undergoing aortic valve replacement in the current period (1973 to 1980) 73%, compared to 67% during the years 1960 to 1972. The study of Starr is an actuarial analysis and is prone to the errors of such analyses. Data from remote periods with more complete follow-up and larger numbers may not be strictly comparable to more recently acquired data. The 5 and 10 year survival with the Bjork-Shiley tilting-disc prosthesis (Bjork 1979, Karp 1981) and the 5 year survival with the porcine heterograft (Oyer 1979, Oyer 1980, Cohn 1981), are similar to survival data with the Starr-Edwards caged-ball prosthesis.

The second study by McGoon et al (McGoon 1984) from the Mayo Clinic, evaluated the 10 to 19 year follow-up in 336 patients with severe symptomatic valvular regurgitation in whom a Starr-Edwards caged-ball prosthetic valve was implanted between 1962 and 1971. Early mortality was 10% for patients with aortic regurgitation and advanced functional disability. The causes were evenly distributed between inability to wean from cardiopulmonary bypass, embolic events, infections, haemorrhage and aortic dissection. Late mortality by actuarial survival curves was highest in the

first year (16%), remaining high for the first 3 years at which point actuarial survival was 69%. Death during this period probably represented a combination of a technically imperfect operative result and advanced irreversible myocardial dysfunction. The mortality declined until the 6th year postoperatively and then stabilised at the same rate as that of an age- and sex- matched general population. At 15 years, survival was 40%, which is comparable to other longterm studies (Macmanus 1978, Teply 1981). Despite the lack of controlled trials, the survival curve of operated patients shows a definite improvement over survival rates of comparable patients without surgery (Spagnuolo 1971, Munoz 1975, McGoon 1981). The mode of late death was sudden in 27% of cases, followed by emoblic events in 16%, myocardial infarction in 15%, unknown in 12%, congestive heart failure in 10% and infection or prosthetic valve complications in 6% each. Although rhythm disturbances in patients with severe aortic regurgitation have not been thoroughly investigated until now, a high incidence of frequent and complex ventricular arrhythmias have been recorded during ambulatory monitoring (Hochreiter 1982, von Olshausen 1983). A recently reported study by von Olshausen et al (von Olshausen 1984) indicated that repetitive ventricular arrhythmias (Lown grade 4A and B) were infrequent in patients with normal left ventricular ejection fraction before and late after aortic valve replacement. In contrast, in patients with impaired left ventricular ejection fraction, complex ventricular premature beats are common pre-operatively, but the postoperative improvement in left ventricular function was usually accompanied by a significant reduction in the grade of the ventricular premature contractions. In addition,

although the frequency of postoperative sudden death varies considerably in different studies from between 6% to more than 50% (Hirschfeld 1974, Copeland 1977, Samuels 1979, Turina 1984), its recognition as a factor in late causation of death following valve replacement for severe aortic regurgitation emphasises the need to detect and treat arrhythmias and eliminate arrhythmogenic factors in the management of the postoperative patient (McGoon 1984, Turina 1984).

In addition, although the durability of the Starr-Edwards valve is high and symptomatic status is improved in approximately 80% of patients by at least one functional class (with 40% asymptomatic), thromboembolism remains a major problem with almost half (44%) of patients having sustained a systemic embolic event by 15 years of follow-up. Seventeen percent of patients sustained multiple events with cerebral events (80%) being the most frequent.

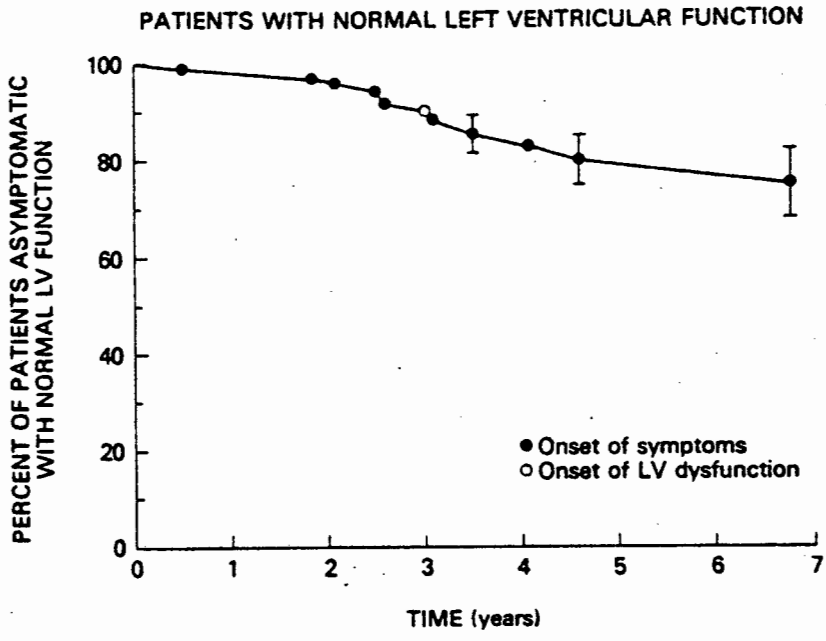
II.2.0 THE NATURAL HISTORY OF SEVERE ASYMPTOMATIC AORTIC REGURGITATION AND NORMAL LEFT VENTRICULAR FUNCTION:

It is suggested that symptomatic patients with severe aortic regurgitation and impaired left ventricular systolic function are at risk of irreversible myocardial dysfunction and death from congestive heart failure following successful aortic valve replacement (Cunha 1980, Forman 1980, Henry 1980, Greves 1981). However, within the subgroup with pre-operative left ventricular dysfunction, those with less marked symptoms (Cunha 1980, Greves 1981), preserved exercise capacity (Bonow 1980), and shorter duration of pre-operative left ventricular dysfunction (Bonow 1984) have a better prognosis and greater likelihood of improvement.

Nevertheless, because of the fear of irreversible left ventricular dysfunction, some authors have recommended aortic valve replacement in all patients wtih severe aortic regurgitation, even if asymptomatic with preserved left ventricular systolic function (Kirklin 1973, Isom 1974, Smith 1976). This controversial recommendation is not universally accepted and was proposed prior to the detailed description of the natural history of asymptomatic patients with severe aortic regurgitation and normal left ventricular function by Bonow et al (Bonow 1983) in which they emphasised this subset's excellent prognosis with conservative non-operative management. Their study consisted of a serial evaluation of 77 patients with asymptomatic severe aortic regurgitation and normal resting left ventricular systolic function measured non-invasively by echocardiogram (fractional shortening >29%) and radionuclide ventriculography (ejection fraction > 45%). These patients were followed from 6 to 114 months (mean 49 months) with no deaths. Twelve patients required aortic valve replacement. In eleven of these, the indication for surgery was the onset of symptoms, with the development of left ventricular dysfunction occurring 6 - 12 months before or coincident with the onset of symptoms in 5 of the 11 patients. One patient was operated on for progressive left ventricular dysfunction without the development of symptoms when ejection fraction dropped from 61% to 45% and end-systolic diameter increased from 51mm to 58mm over a 36 month follow-up period. All 12 patients had preserved effort tolerance and were able to complete the first stage of the National Institutes of Health protocol(Bonow 1980) without limiting symptoms.

The following life table (Fig. 2.2) depicts the course of the 77 patients, with the onset of symptoms or the onset of left ventricular dysfunction used as end points. At 7 years, 75 ± 7% of the patients remained asymptomatic with normal left ventricular function:-

Figure 2.2 LIFE TABLE ANALYSIS IN ASYMPTOMATIC AORTIC REGURGITATION



(Figure 1, Circulation 68;511,1983)

II.2.1 Influence of Initial Left Ventricular Dimensions and Systolic Function on Clinical Course:

Using a Cox univariate life table analysis(Cox 1972) several echocardiographic parameters were identified which predicted the subsequent development of symptoms or left ventricular dysfunction. These are summarised in Table 2.2. Rest ejection fraction(EF) determined by equilibrium radionuclide angiocardiography (ERNA) was

not a significant predictor but peak exercise ejection fraction and the magnitude of change in ejection fraction from rest to peak exercise (functional reserve) were both predictive of the subsequent clinical course.

Table 2.2 VARIABLES ON INITAL STUDY ASSOCIATED WITH SUBSEQUENT SYMPTOMS OF LEFT VENTRICULAR DYSFUNCTION

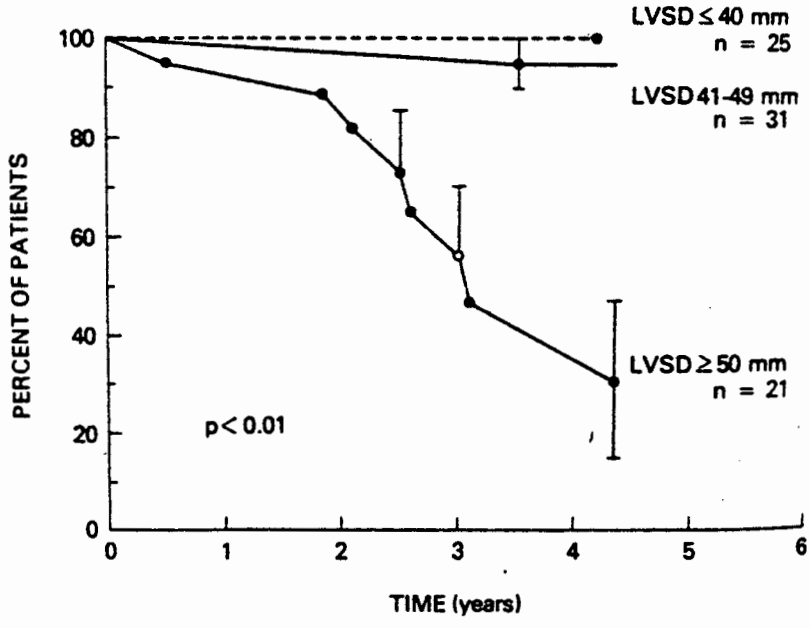
Variable	p value
Echocardiographic data	
LV fractional shortening	< .01
LV end-systolic dimension	< .01
LV end-diastolic dimension	< .01
Radionuclide angiographic data	
LV EF at rest	NS
LV EF during exercise	< .01
LV EF response to exercise	< .01

(Table I, Circulation 68;512,1983)

Patients with an end-systolic dimension (DES) of > 50mm (21 patients) had a significantly greater likelihood of developing symptoms or left ventricular dysfunction. Only 31% of such patients were asymptomatic at 4.5 years of follow-up. In contrast, no patient with an initial end-systolic dimension of < 40mm developed symptoms during this follow-up period.

The following figure (2.3) shows the influence of the initial left ventricular end-systolic dimension on the subsequent clinical course.

Figure 2.3: INFLUENCE OF INITIAL LEFT VENTRICULAR END-SYSTOLIC DIMENSION ON SUBSEQUENT CLINICAL COURSE.

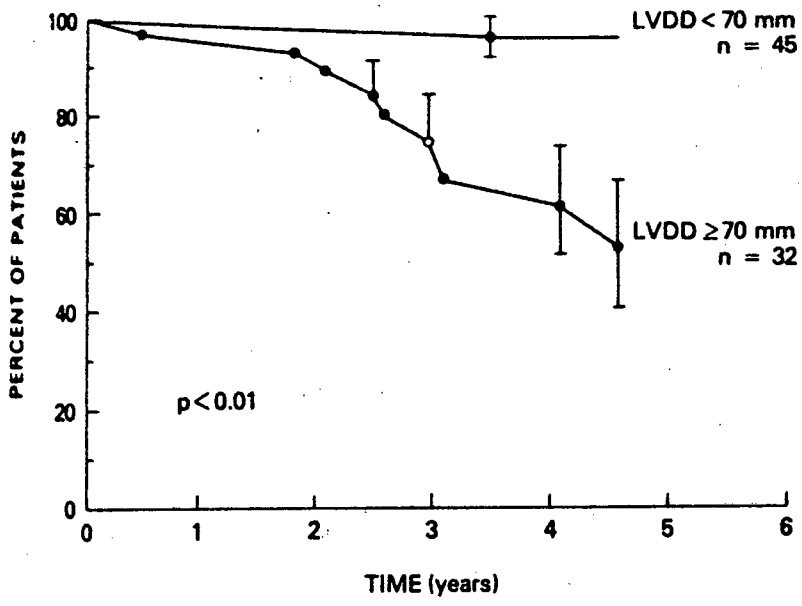


(Figure 4, Circulation 68;512,1983)

Similarly end-diastolic diameter (DED) at the time of initial evaluation was predictive. Fifty three of seventy seven patients had an initial LVDED > 70mm and developed symptoms during the follow-up period. This is shown in figure 2.4.

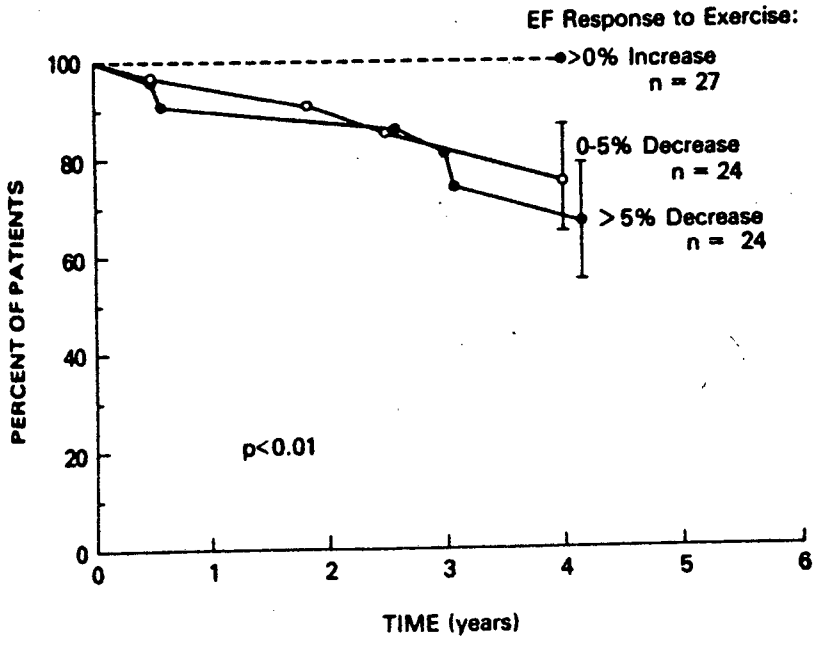
Similar but less significant trends were observed when patients were stratified on the basis of either peak exercise ejection fraction or functional reserve (change in ejection fraction on exercise) and are summarised in figure 2.5. No patients who increased their ejection fraction on exercise required surgery compared to those with a drop in ejection fraction (irrespective of the magnitude), of whom one third came to operation within 4 years.

Figure 2.4 INFLUENCE OF INITIAL LEFT VENTRICULAR END-DIASTOLIC DIMENSION ON SUBSEQUENT CLINICAL COURSE.



(Figure 5, Circulation 68;513,1983)

Figure 2.5 INFLUENCE OF INITIAL LEFT VENTRICULAR EJECTION FRACTION RESPONSE TO EXERCISE ON THE SUBSEQUENT CLINICAL COURSE



(Figure 6, Circulation 68;513,1983)

Thus the ejection fraction response to exercise was significantly associated with subsequent clinical course when this variable was analysed as a continuous function by the Cox model.

II.2.2 Relationship of Ejection Fraction Response to Exercise and Resting Echocardiographic Dimensions:

With increasing echocardiographic systolic and diastolic dimensions at rest, there was a progressive increase in the number of patients who had a fall in ejection fraction on exercise:-

DES < 40mm - 35% patients had a drop in EF on exercise

DES 41-49mm - 62% patients had a drop in EF on exercise.

DES > 50mm - 90% patients had a drop in EF on exercise.

DED < 60mm - 29% patients had a drop in EF on exercise.

DED 61-69mm - 54% patients had a drop in EF on exercise.

DED > 70mm - 82% patients had a drop in EF on exercise.

The correlation coefficients between functional reserve and resting systolic and diastolic dimensions were significant ($p < 0.01$) and it is thus uncertain whether ejection fraction response to exercise provides added prognostic information. Statistically this could not be proven by a stepwise Cox regression, but small sample size and limited end points precluded a firm conclusion.

II.2.3 Change in Left Ventricular Dimensions and Function:

Despite a statistically non-significant change in end-diastolic diameter in both the stable and operated groups at initial and late (6-8 months postoperatively) evaluation, an increase of > 5mm was observed in 11 patients.

End-systolic dimension did increase significantly in both groups

with time, with 5 out of 12 patients whose dimensions increased by > 5mm developing symptoms or left ventricular dysfunction.

Fractional shortening, in contrast, only decreased significantly in the group undergoing aortic valve replacement.

Although radionuclide ejection fraction at rest decreased significantly in both groups, with 8 of 12 patients with a drop in ejection fraction to < 50% developing symptoms, functional reserve showed great variability between early and late studies and did not change significantly in either group.

II.2.4 Results of Aortic Valve Replacement:

These were extremely encouraging with no operative or peri-operative deaths. Most patients were re-evaluated 6-8 months postoperatively, with end-diastolic diameter returning to normal (< 55mm) in 75% of cases - 10 of the 12 patients undergoing valve replacement had a pre-operative end-diastolic diameter of > 70mm. This is important prognostically since previous studies indicate that patients with persistent left ventricular dilatation (> 70mm) postoperatively, are at increased risk of death from congestive heart failure (Gaasch 1978, Bonow 1980, Clark 1980, Henry 1980). There was an associated improvement in systolic pump function with rest ejection fraction normalising in all patients (> 45%), peak exercise ejection fraction increasing from 36 $\pm$ 7% to 56 $\pm$ 15% and a concomitant improvement in functional reserve.

II.3.0 THE PRE-SYMPTOMATIC DEVELOPMENT OF LEFT VENTRICULAR DYSFUNCTION:

Despite these apparently reassuring conclusions, there remains the clinical problem of a group of patients who develop left ventricular dysfunction prior to the onset of symptoms. It is not known (i) how frequently this occurs, (ii) whether this can be predicted in individual patients (iii) whether left ventricular dysfunction can be stabilised, improved or preserved by valve replacement and (iv) whether patient survival will be better with or without aortic valve replacement.

Among the studies claiming benefit with earlier surgery are the following. None are perfect:-

(i) Spagnuolo et al (Spagnuolo 1971) identified a "high risk" triad in young patients with rheumatic aortic regurgitation with an eighty seven percent risk of angina, heart failure or death within 6 years. It was not clearly stated whether the development of angina or heart failure resulted in a poor postoperative outcome.

(ii) Smith et al (Smith 1976), using data based on the incidence of death before aortic valve replacement, did not report a favourable influence of aortic valve replacement in any subgroup of patients studied, and

(iii) Braun et al (Braun 1973), reported that the prognosis after aortic valve replacement was related to a pre-operative cardio-thoracic ratio of greater than 0.56. The problem with this study was that only operated patients were compared, the majority had aortic stenosis and thus it

compared aortic stenosis with mixed aortic valve disease.

In addition, it has been assumed that the asymptomatic patient with severe aortic regurgitation will only become symptomatic with the onset of left ventricular dysfunction, thus making it "too late" if symptoms are used as the only indication for surgery. However, it is important to appreciate that the onset of symptoms is not necessarily always associated with the onset of left ventricular systolic dysfunction (Greves et al 1980), and thus symptoms cannot be automatically attributed to impaired resting left ventricular systolic function. Furthermore, Schwarz and Clark (Schwarz 1979, Clark 1980) have shown that in symptomatic patients with impaired systolic function, aortic valve replacement can be performed with a low operative mortality; a 3 year survival of 60-70% with functional class improved or maintained in late survivors; there was an associated significant but usually incomplete regression of left ventricular dilatation and hypertrophy with normalisation of the left ventricular end-diastolic pressure (16 $\pm$ 3mmHg to 10 $\pm$ 2mmHg) and an improvement in systolic function in 50% of cases.

In conclusion, in asymptomatic patients with severe aortic regurgitation and resting systolic dysfunction or rapidly progressive cardiac enlargement aortic valve replacement is usually considered to be clinically indicated, although it is accepted that this recommendation is not based on firm data. Improved medical management e.g. chronic vasodilator therapy (Greenberg 1980, Greenberg 1980, McKay 1983, Shen 1984) has been suggested and is being evaluated but has not, as yet, been accepted as a therapeutic option. The development of "perfect" prosthetic

devices that are haemodynamically sound, do not suffer mechanical failure or degeneration, are free of thromboembolic complications without the need for long term anticoagulants and do not damage the blood cells, may similarly change clinical practice. Twenty five years after implantation of the first prosthetic valves, advances and improvements in valve design have been minor.

11.4.0 THE NON-INVASIVE EVALUATION OF LEFT VENTRICULAR FUNCTION IN SYMPTOMATIC PATIENTS WITH SEVERE AORTIC REGURGITATION: ECHOCARDIOGRAPHIC AND RADIONUCLIDE MARKERS OF POOR POST-OPERATIVE SURVIVAL:

Aortic root and left ventricular cineangiography have been the "gold standard" for defining the severity of aortic regurgitation and its effect on left ventricular performance - however, serial follow-up by these means is impractical. More recently non-invasive measures of left ventricular size (echocardiography) and function (echocardiography and equilibrium radionuclide angiocardiography) have been serially utilised in an attempt to optimise the timing of surgery by formulating pre-operative markers of left ventricular dysfunction and poor postoperative survival. In these endeavours, the thinking has been clouded by a tendency to equate the two and failing to appreciate that apparent pre-operative left ventricular dysfunction may be rapidly reversible by aortic valve replacement and the consequent changes in LV loading conditions.

II.4.1 Impaired Systolic Function at Rest

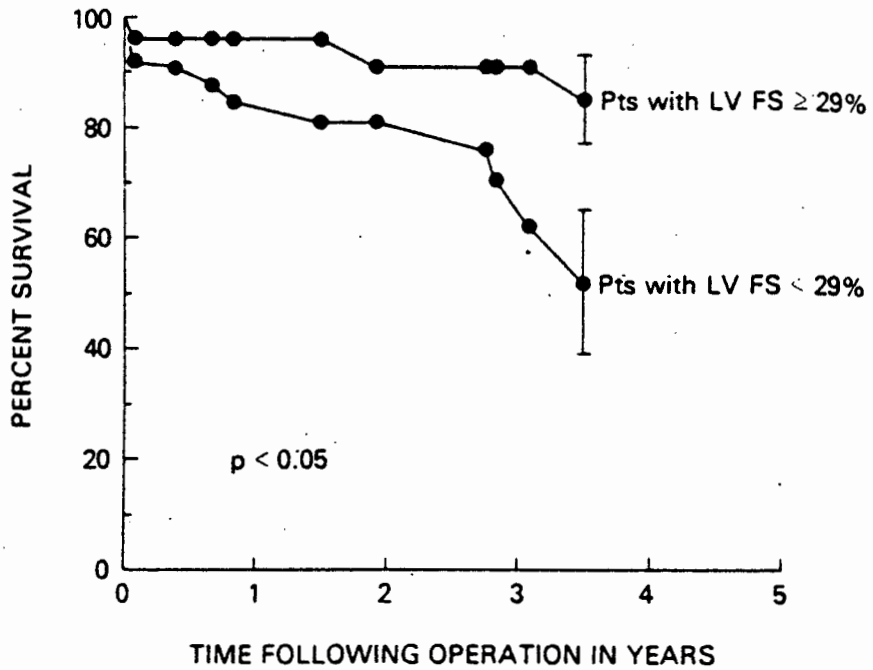
The normal response to chronic volume overload is chamber

dilatation with compensatory hypertrophy, associated with a normal extent of systolic wall shortening per unit of circumference and thus preserved ejection fraction (Ross 1972, Ross 1981). As in other forms of mechanical overload, if preload reserve is fully utilised and afterload is excessive for the degree of hypertrophy, the ejection fraction may be reduced i.e. "áfterload mismatch" can result in reduced left ventricular performance without necessarily being accompanied by reduced contractility (Ross 1976). The ventricle will resume normal shortening and ejection as soon as the excess load is removed by aortic valve replacement. Usually compensatory mechanisms lead to an appropriate extent of hypertrophy to match the increased load, and in doing so wall stress is normalised. Impaired resting pre-operative ejection fraction, measured either non-invasively using echocardiographic fractional shortening (Cunha 1980, Henry 1980) or angiographically by left ventricular ejection fraction (Cohn 1974, Fishl 1977, Forman 1980, Greves 1981) often represents depressed myocardial contractility and thus may predict which symptomatic patients are at risk of death from congestive heart failure after technically successful aortic valve replacement. At the National Institutes of Health between 1972 and 1978 patients with a suboptimal fractional shortening `of less than 29% had a 3 year survival of 62% compared to 91% in patients with normal fractional shortening (Henry 1980). In those patients with severely depressed systolic function (fractional shortening < 25%), 3 year survival was only 42%. These results are graphically displayed in figure 2.6.

Comparable data are reported by Cunha (Cunha 1980), using a fractional shortening of < 30% (4 year survival 77% versus 96%).

In a study from our own institution (Forman 1980), the effect of pre-operative left ventricular ejection fraction and other

Figure 2.6 SURVIVAL AFTER OPERATION FOR AORTIC REGURGITATION FROM 1972 TO 1978



(Figure 2, Am J Cardiol 50;326,1982)

variables on postoperative survival was examined in 279 patients after isolated aortic valve replacement between August 1972 and February 1978. During the initial period Lillehei-Kaster prostheses were used but discontinued because of unsatisfactory results (Forman 1977). Subsequently the Starr-Edwards model 2400 prosthesis or the Bjork-Shiley prosthesis were used for patients with large and small aortic roots respectively. Later the glutaraldehyde - preserved procine heterograft was used. In contrast to patients with aortic stenosis or mixed aortic valve disease, patients with aortic regurgitation and a pre-operative

left ventricular ejection fraction (LVEF) of <50% had a significantly worse 3 year survival rate (64 ± 10%) than those patients with a LVEF > 50% (91 ± 8% ($p < 0.02$). In addition a reduced cardiac index < 2.5 litres/minute per M^2 also significantly predicted a reduced 3 year survival compared to patients with a normal cardiac index ($p < 0.02$). The operative mortality of 3.5% was not affected by any pre-operative variable studied. Nine of the twenty-two late deaths occurred in the group with pure aortic regurgitation, 56% due to congestive heart failure, and one patient each due to embolism, myocardial infarction, infective endocarditis and sudden death. The recommendation was to monitor LVEF non-invasively in patients with aortic regurgitation and to advise valve replacement before ejection fraction became severely depressed.

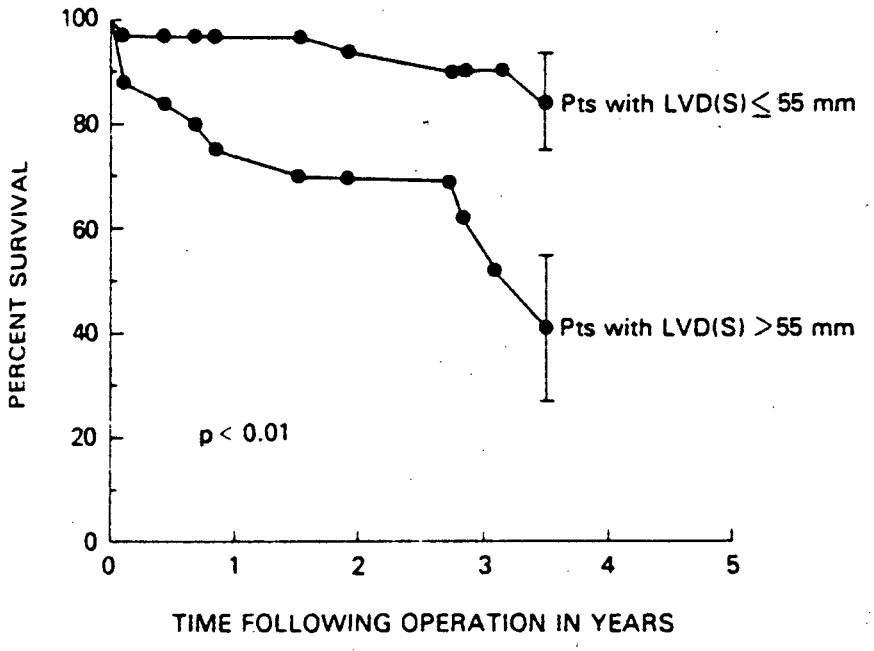
II.4.2 Echocardiographic End-Systolic Diameter (DES):

Henry (1980), using an end-systolic diameter greater than 55mm was able to identify a high risk group of patients undergoing aortic valve replacement with a 3.5 year survival of 40%. In contrast, those with a DES < 55mm had a 3.5 year survival of 80%. These results are summarised in figure 2.7. It is important to note that 56% of deaths (5 out of 9) occurred in the immediate postoperative period.

This study is compatible with the data from Cunha (1980) and the angiographic study of Borow (1980) and in agreement with the report from Grossman (1977) characterising the contractile state of the left ventricle by end-systolic volume and thus subgrouping patients according to their left ventricular function.

In contrast, Turina and Krayenbuehl (1979) reported that postoperative results could not be predicted from the M-mode echocardiogram, including an DES greater than 55mm.

Figure 2.7 SURVIVAL AFTER OPERATION FOR AORTIC REGURGITATION FROM 1972 TO 1978 BASED ON PRE-OPERATIVE ECHOCARDIOGRAPHIC DES



(Figure 3, Am J Cardiol 50;327,1982)

II.4.3 Echocardiographic End-Diastolic Diameter (DED):

This dimensional measure is less sensitive than the pre-operative DES, but does identify a small subgroup of patients with severe ventricular dilatation (DED > 80mm) who are at increased risk postoperatively of persistent left ventricular dilatation and subsequent development of congestive heart failure (Gaasch 1978, Clark 1980, Henry 1980, Stone 1984). Survival analysis has not been calculated in this subset of patients because of the small numbers of patients in all reported series. It would appear that this dimension is a marker of very severe left ventricular

dilatation and of little practical clinical value.

II.4.4 Radius to Wall Thickness Ratio (Wall Stress):

The prognostic implications of the end-diastolic diameter can be refined by evaluating the degree of associated compensatory left ventricular hypertrophy. This results in a normalisation of wall stress (Gould 1974, Grossman 1975, Gaasch 1979, Kumpuris 1982). The ratio of end-diastolic radius to posterior wall thickness thus serves as a measure of appropriate left ventricular muscle mass for a given chamber volume (volume to mass ratio).

In a number of studies (Gault 1970, Gaasch 1978, Osbakken 1981, Kumpuris 1982) this pre-operative ratio was a strong predictor of subsequent postoperative regression of left ventricular hypertrophy and a reduction in left ventricular dimension. An increased pre-operative ratio of > 4, reflected inadequate hypertrophy with increased wall stress and was associated with persistent postoperative dilatation and congestive heart failure. Because few patients in the reported series have a very high pre-operative ratio (similar to a DED > 80mm), this index appears to be very insensitive in identifying the majority of patients at risk.

In addition, in contrast to the above studies, Cunha (1980) found no predictive value in this ratio. Thus, although conceptually attractive, the integration of dilatation, hypertrophy and contractile function expressed as wall stress, has not been demonstrated to be a pre-operative predictor of long term outcome in the majority of patients with severe aortic regurgitation.

II.4.5 Exercise Equilibrium Radionuclide Angiocardiography (ERNA): This form of investigation has been utilised in an attempt to refine the prognostic implications of resting left ventricular systolic function by detecting early, reversible myocardial dysfunction. Although Borer (1978) has shown that the majority of patients with symptomatic aortic regurgitation have an abnormal ejection fraction response to maximum supine exercise despite normal resting values, no level is clearly associated with either impaired postoperative survival or irreversibility of left ventricular dysfunction (Borer 1979, Bonow 1980). There is growing evidence to suggest that exercise - induced left ventricular dysfunction is reversible postoperatively. In a consecutive study of 43 patients with symptomatic aortic regurgitation undergoing valve replacement between 1976 and 1980 and re-evaluation 6 months postoperatively, 93% of patients had a postoperative peak exercise ejection fraction greater than their pre-operative value, and 40% of those with a subnormal pre-operative exercise ejection fraction normalised postoperatively. Neither the postoperative ejection fraction nor the change in ejection fraction from the pre-operative to the postoperative value could be predicted by the pre-operative exercise ejection fraction. These results are summarised in figure 2.8.

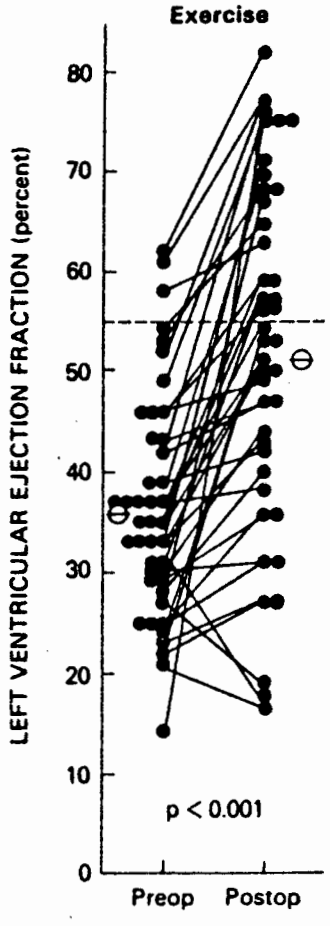
A more detailed discussion on the exercise evaluation of patients with severe aortic regurgitation will follow.

II.4.6 Exercise Capacity:

This parameter is used both as a measure of cardiac reserve and as a quantitative measure of functional class, being less subjective

than the New York Heart Association classification (NYHA 1979). In the series reported by Bonow (Bonow 1980), exercise capacity did not correlate with echocardiographic dimensions or systolic

Figure 2.8 CHANGE IN LVEF DURING EXERCISE FROM PRE-OP TO POSTOP VALVE REPLACEMENT



(Figure 4, Am J Cardiol 50;329,1982)

function measured non-invasively. Many patients had an excellent exercise tolerance despite severe left ventricular dysfunction, thus confirming the observation that patients with severe aortic regurgitation and left ventricular dysfunction may indeed be asymptomatic (Lewis 1970, Goldschlager 1973, Karaian 1980). In

summary:-

(i) Exercise capacity appears to be an independent measure of cardiac reserve not reflected in the usual indices of left ventricular systolic function (Benge 1980, Franciosca 1981, Litchfield 1982) and in the above series, only one patient who completed stage 1 of the National Institutes of Health protocol died 61 months postoperatively compared to an operative mortality of 11% and a 3 year mortality rate of 32% in the group with poor exercise tolerance. This dissociation between exercise capacity and measured LV function is well recognised in LV dysfunction due to other causes and explained by compensatory tachycardia and utilisation of preload reserve (Benge 1980).

The following table (2.3) summarises the National Institutes of Health exercise protocol.

Table 2.3 NIH EXERCISE PROTOCOL

	Stage I		Stage II	
Time (min)	Speed (mph)	Grade	Speed (mph)	Grade
0	2.2	0%	1.9	10%
2.5	2.2	2.5%	2.3	12%
5.0	2.2	5.0%	2.7	14%
7.5	2.2	7.5%	3.1	16%
10.0	2.2	10.0%	3.5	18%
12.5	2.2	12.5%	3.9	20%
15.0	2.2	15.0%	4.7	20%
17.5	2.2	17.5%	5.5	20%
20.0	2.2	20.0%	6.3	20%
22.5	End of Stage I	End of Stage I	7.1	20%

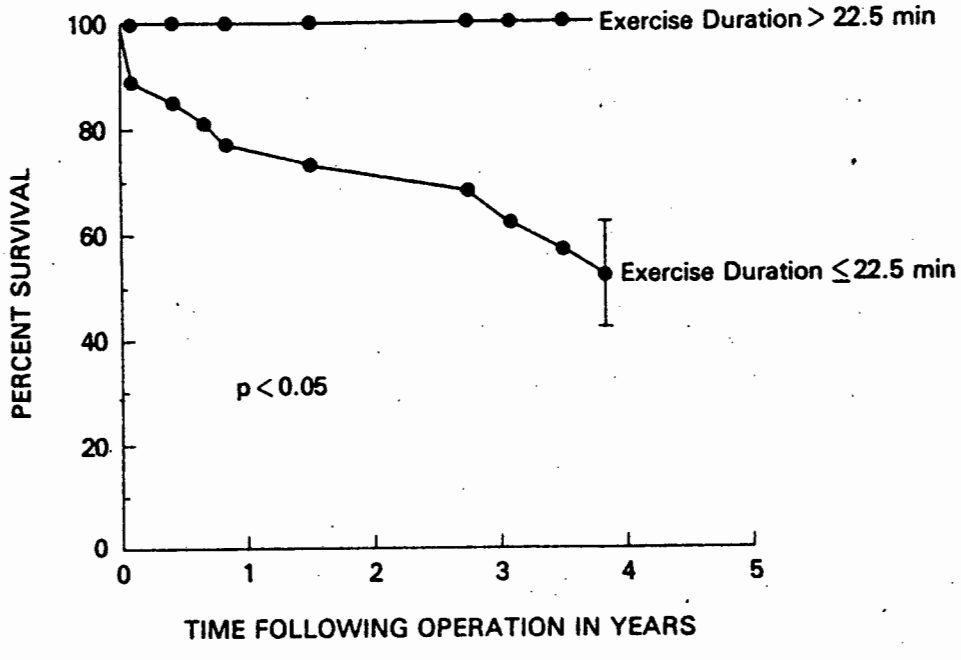
(Table 1, Circulation 62;1282,1980)

(ii) The combined analysis of exercise capacity and left

ventricular systolic function further refines the prognostic subgroups, with those patients who have preserved exercise tolerance despite impaired systolic function at rest having an excellent long term prognosis compared to the group with poor effort tolerance and impaired resting systolic function. This is summarised in figure 2.10 with the numbers in italics indicating the patients at risk at each time interval.

The following graph (figure 2.9) displays the postoperative survival based on pre-operative exercise capacity.

Figure 2.9 POSTOPERATIVE SURVIVAL AND PRE-OP EXERCISE CAPACITY

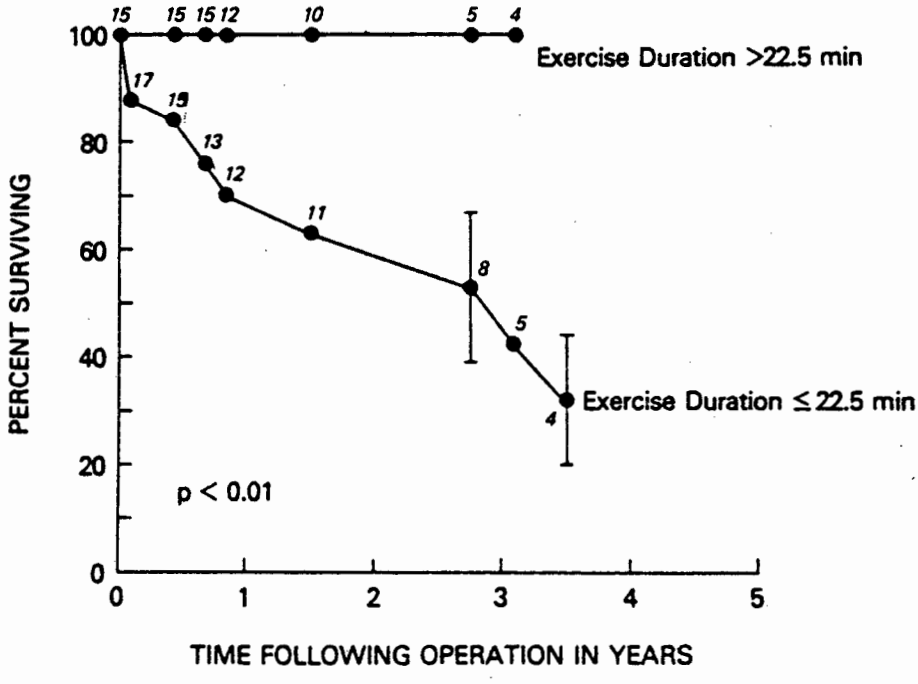


(Figure 5, Am J Cardiol 50;329,1982)

This work by Bonow (1980) is substantiated by the work of Cunha (1980) and Greves (1981) who showed improved late postoperative

survival in those patients with left ventricular dysfunction and New York Heart Association functional class one and two (compared to class 3 and class 4).

Figure 2.10 SURVIVAL AFTER OPERATION FROM 1972 TO 1978 IN 32 PATIENTS WITH SUBNORMAL PRE-OPERATIVE FS, SUBGROUPED ON THE BASIS OF PRE-OPERATIVE EXERCISE CAPACITY



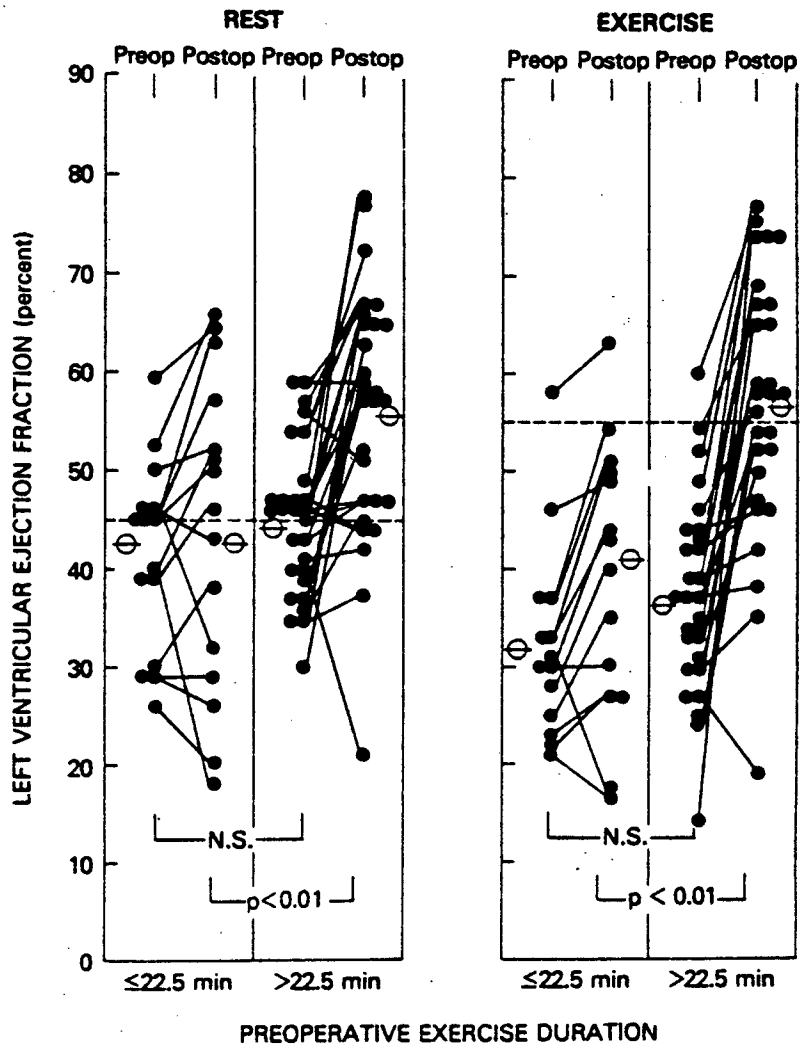
(Figure 6, Am J Cardiol 50;330, 1982)

(iii) It also proves helpful in predicting the reversal of left ventricular dysfunction, with those patients who have a preserved exercise capacity demonstrating a greater postoperative reduction in left ventricular end-diastolic dimension and a significantly higher postoperative resting and peak exercise ejection fraction (Bonow 1980). This change in LV ejection fraction from pre-operative to 6

months postoperative in symptomatic patients operated on between 1976 and 1981 subgrouped on pre-operative exercise capacity is summarised in the figure overleaf.

Thus, in symptomatic patients with impaired pre-operative resting left ventricular systolic function, preserved exercise capacity rather than the ejection fraction is predictive of normalisation of

Figure 2.11 CHANGE IN REST AND EXERCISE LVEF POSTOPERATIVELY STRATIFIED ON THE BASIS OF PRE-OPERATIVE EXERCISE CAPACITY



(Figure 8, Am J Cardiol 50;331,1982)

postoperative left ventricular systolic function.

II.4.7 Postoperative Echocardiographic End-Diastolic Dimension(DED): In contrast to pre-operative end-diastolic diameter, its postoperative measurement has considerable prognostic value, with persistent postoperative dilatation of greater than 70mm identifying a significant number of patients at risk of subsequent death from congestive heart failure (Gaasch 1978, Clark 1980, Henry 1980). These reports are consistent with an earlier report of cardiac dimensions on chest X-ray which showed that failure of cardio-thoracic ratio to decrease following aortic valve replacement was associated with a subsequent poor prognosis (Hirshfeld 1974). The reduction in end-diastolic dimension occurs early, i.e. between 2 weeks and 2 months postoperatively (Venco 1976, Gaasch 1978, Schuler 1979, Henry 1980), with little further change at late follow-up evaluation (Gaasch 1978, Schuler 1979, Henry 1980). The reduction in dimension may be predicted by the pre-operative end-systolic dimension and fractional shortening (Clark 1980, Henry 1980, Kumpuris 1982, Stone 1984). These echocardiographic studies have been substantiated by both contrast angiography (Borow 1980) and radionuclide ventriculography (Boucher 1981).

In conclusion, the results of surgery including postoperative survival, reversal of left ventricular dilatation and hypertrophy, or the development of congestive heart failure following valve replacement for symptomatic aortic regurgitation can be predicted from non-invasive pre-operative evaluation of LV size, systolic function, wall stress and preserved exercise capacity. These

markers are more sensitive than haemodynamic variables in identifying patients at risk (Henry 1980), and although systolic dysfunction at rest is a sensitive predictor of ultimate outcome, it is not specific, with improvement and even normalisation of left ventricular systolic function frequently occurring despite severe pre-operative depression of systolic function (Kennedy 1977, Gaasch 1978, Borer 1979, Herreman 1979, Schuler 1979, Schwartz 1979, Bonow 1980, Clark 1980, Ross 1981).

II.5.0 THE NON-INVASIVE EVALUATION OF LEFT VENTRICULAR FUNCTION IN ASYMPTOMATIC AORTIC REGURGITATION:

II.5.1 Echocardiographic Systolic Size and Function at Rest:

Against this background, serial non-invasive echocardiographic assessments of left ventricular systolic size and function appeared to be potentially useful in helping to optimise the timing of surgery in asymptomatic patients with left ventricular dysfunction. Two studies are particularly relevant in this regard (Henry 1980, McDonald 1980). A total of 50 asymptomatic patients with severe aortic regurgitation (37 patients from the National Institute of Health and 13 patients from the Univesity of Melbourne) underwent serial M-mode echocardiographic follow-up. Twenty six percent (26%) of these patients had an end-systolic dimension greater than 55mm, and 36% had a fractional shortening of less than 29% i.e. a significant abnormality of left ventricular systolic dimension associated with evidence of systolic dysfunction.

Life table analysis, using the onset of symptoms as the end-point, showed that two-thirds of asymptomatic patients with this abnormality required aortic valve replacement during a 3 year

follow up period because of the development of symptoms. Thus, the time between the demonstration of left ventricular systolic dysfunction and the onset of symptoms is short.

It thus appears reasonable to consider aortic valve replacement in this subset of asymptomatic patients before the onset of symptoms - this conclusion has been substantiated by observations that asymptomatic patients with left ventricular dysfunction have improved late postoperative survival compared to the severely symptomatic group (Cunha 1980, Greves 1981).

II.5.2 Limitations in the Use of M-mode Echocardiography:

However, decisions should not be based on a single echocardiographic measurement. Although it is an excellent technique for the measurement of left ventricular dimensions and fractional shortening in patients with left ventricles of normal dimension, its limitations in severe left ventricular dilatation need to be appreciated. When the left ventricle is dilated and if contractile function is impaired:-

(i) the ventricular geometry changes from an ellipsoid to a more spherical shape (Gould 1974, Linhart 1975, Johnson 1976, Fischl 1977, Abdulla 1980).

(ii) abnormal apex to base shortening occurs (Gould 1976, Hecht 1981, Osbakken 1981),

(iii) Regional contraction abnormalities may develop, thereby limiting M-mode echocardiography in the assessment of left ventricular dimensions and global systolic function. When compared to angiographic indices (Johnson 1976, Bhatt 1978, O'Rourke 1980), the echocardiogram consistently

underestimates dimensions and overestimates contractile function. The degree of LV dysfunction may thus be more severe than the echocardiogram suggests.

Despite the above concerns, this view is not universally held. Vandenbossche and others (1984) recently correlated M-mode echocardiographic measurements of left ventricular size and function in patients with chronic severe aortic regurgitation with measurements obtained from a nongeometric method using gated blood pool radionuclide angiography. They used a corrected cube formula and located the M-mode beam more adequately under two-dimensional control. This approach provided a practical and convenient way of improving the M-mode evaluation of left ventricular shape and function.

Other limitations include the following:-

(i) Minor changes in patient position or transducer angulation may cause errors in left ventricular dimension measurement of up to 20%, although calculation of fractional shortening is less variable (Linhart 1975, Popp 1975).

(ii) Postoperative assessment of overall left ventricular function is subject to considerable error due to paradoxical septal motion which occurs in $\pm$ 90% of cases (Burggraf 1975, Righetti 1977). Recent work has suggested that such abnormal motion of the interventricular septum appears to be a motion artifact caused by exaggerated systolic anteromedial translation of the entire heart within the chest, as viewed from a fixed external frame of reference

(Kerber 1982, Waggoner 1982, Force 1983). Force et al (1984), using quantitative two-dimensional echocardiographic analysis of regional wall motion in patients with perioperative myocardial infarction following coronary artery bypass surgery, demonstrated that floating-axis analysis, by correcting the abnormal motion of the septum and normalising the apparently enhanced motion of the lateral wall of the left ventricle, was more accurate and clinically relevant in the evaluation of these patients.

(iii) Dimensional and ejection phase measurements are only as good as the echocardiogram from which they are measured - the requirement is a high-class left ventricular echocardiogram.

In addition, there are conflicting reports on the reproducibility of serial evaluation, with McDonald (1980) reporting limited reproducibility in individual patients, but Clark (1980) maintaining that both dimensions and fractional shortening are reproducible and valuable in documenting deterioration.

II.5.3 Radionuclide Ejection Fraction at Rest:

This index of left ventricular systolic function is independent of left ventricular geometry and thus useful in those patients in whom serial echocardiographic studies are technically inadequate or poorly reproducible.

Normal values, correlation with contrast angiography, reproducibility and intra- and inter-observer variation have been investigated in our own laboratory (see Appendix II) and in others (Bacharach 1979, Okada 1980, Machac 1984) and found to be

satisfactory.

II.5.4 Radionuclide Ejection Fraction Response to Exercise:
The rationale behind this form of assessment is the fact that because resting left ventricular systolic function is such a sensitive predictor of long term prognosis, stress induced dysfunction may represent early, reversible myocardial dysfunction and thus help in the selection of asymptomatic patients for valve replacement surgery before the onset of irreversible dysfunction (Bolen 1976, Ross 1976, Borer 1978). A number of methods of stressing the left ventricle have been proposed, including angiotensin infusion (Bolen 1976), incremental atrial pacing (Firth 1982), isometric handgrip exercise (Fisher 1973, Gumbiner 1983, Gordon dePuey 1984) and supine and erect bicycle exercise (Borer 1978, Poliner 1980, Dehmer 1981, Lewis 1982, Peter 1982, Huxley 1983). Using supine bicycle exercise, Borer (1978) reported a drop in exercise ejection fraction in two-thirds of asymptomatic patients with severe aortic regurgitation. Thus, abnormal exercise reserve, i.e. a drop in ejection fraction on exercise, appears early in the natural history of the disease, predating symptoms or resting left ventricular systolic dysfunction. However, the exercise response in patients with aortic regurgitation is variable. There is a reduction in regurgitant fraction with exercise (Levinson 1970, Ettinger 1972), variable changes occur in end-diastolic volume, end-systolic volume and ejection fraction (Borer 1978, Dehmer 1981) due to the fact that volume changes are significantly influenced by the complex interaction of changes in heart rate, preload and afterload (Karliner 1974, Ranklin 1975, Ross 1976, Boucher 1981, Ross 1981). In turn these variable

responses depend on the severity and type of exercise (Epstein 1967, Thadani 1978). Although a decrease in functional reserve may thus represent the unmasking of early, reversible myocardial dysfunction in some patients, in others it may merely reflect altered loading conditions in a severely volume-overloaded ventricle (Ross 1976). It would therefore appear that a decrease in functional reserve is too sensitive a marker, as it occurs very early in the natural history of asymptomatic severe aortic regurgitation (Henry 1979), usually preceding systolic dimensional changes of greater than 50mm at a time when fractional shortening or ejection fraction are normal at rest. Should symptoms develop in this subset, long term prognosis is excellent (Henry 1980). In addition, no absolute level of pre-operative exercise ejection fraction has been demonstrated to be associated with irreversible postoperative dysfunction or impaired postoperative survival.

Defects in many of the above quoted studies include:-

(i) the presence of aortic regurgitation was not proven by aortic angiography in all patients evaluated,

(ii) the severity of the aortic regurgitation was not documented by cine aortography in all patients,

(iii) as not all patients had invasive studies, some may have had clinically undetected coronary artery disease and thus some of the responses to exercise may have been due to exercise - induced ischaemia rather than simply the response of volume overload due to chronic severe aortic regurgitation.

II.5.5 Frequency of Follow-Up Evaluation and Guidelines for Surgery:

Current recommendations are that the frequency of follow-up

evaluation should probably be based on the echocardiographic measurement of end-systolic diameter, with full awareness of the limitations of this investigation and an appreciation that the end-systolic dimension rarely increases by more than 6mm per year (Henry 1980). The following is thus a reasonable set of recommendations based on current knowledge, with the proviso that individualised decision-making remains the cornerstone of management:-

(i) ASYMPTOMATIC SEVERE AORTIC REGURGITATION WITH A DES <50mm: Annual echocardiogram and a biennial radionuclide ventriculogram. Some 20% of patients in this subgroup will develop symptoms or left ventricular systolic dysfunction and require surgery within a 39 month follow-up period.

(ii) ASYMPTOMATIC SEVERE AORTIC REGURGITATION WITH A DES 50-55mm: Six monthly echocardiogram and an annual radionuclide ventriculogram. Approximately 50% of patients in this subset will develop symptoms and require aortic valve replacement within a 2 year follow-up period. Only 20% will develop an end-systolic dimension of greater than 55mm, and postoperative congestive heart failure is distinctly uncommon, only occurring in 3% of patients.

(iii) ASYMPTOMATIC SEVERE AORTIC REGURGITATION WITH A DES >55mm: The majority (80%) of this subgroup will develop symptoms and require valve replacement surgery within a 39 month follow-up period, at which stage they would constitute a "high risk" group of symptomatic aortic regurgitation with impaired left ventricular function. Thus, in this group of

patients, a confirmed echocardiographic DES of > 55mm repeated within a few weeks, together with a radionuclide ventriculogram and formal cardiac catheterisation is recommended. Unless data from the latter two investigations are in major conflict with the echocardiogram, patients in this category should undergo aortic valve replacement, particularly if they have an associated reduction in fractional shortening to less than 29%.

(iv) SYMPTOMATIC SEVERE AORTIC REGURGITATION:

These patients should undergo aortic valve replacement irrespective of their dimensions or systolic function.

II.6.0 POSTOPERATIVE ASSESSMENT:

The review of postoperative evaluation of patients will be discussed under the following headings:-

(i) the effects of aortic valve replacement on survival.

(ii) rest and exercise radionuclide ventriculography.

(iii) echocardiographic evaluation of left ventricular volume, mass and function following aortic valve replacement.

(iv) postoperative rest and exercise haemodynamic assessment.

II.6.1 The Effects of Aortic Valve Replacement on Survival:

Patient survival after aortic valve replacement depends primarily on patient factors and not necessarily on the types of prosthetic valve used; this despite considerable variation in the haemodynamic characteristics of the various prosthetic and bioprosthetic valves. Even an imperfect prosthesis serves to remove the severe volume load on the left ventricle and provided an adequately sized prosthesis is inserted, minimal obstruction to left ventricular

outflow is produced. The probability of long-term survival and the haemodynamic performance of the various aortic valve prostheses is illustrated in the following tables:-

Table 2.4 PROBABILITY OF LONG-TERM SURVIVAL WITH VARIOUS PROSTHESES

Valve	% 5-Year Survival	% 10-Year Survival
Starr-Edwards	70	60
Bjork-Shiley	82	78
Hancock	82	70
Carpentier-Edwards	87	-
Ionescu-Shiley	88	73

(Table 1, Chest 85 : 391, 1984)

Table 2.5 HAEMODYNAMIC PERFORMANCE OF VARIOUS AORTIC VALVE PROSTHESES

Prosthesis	PSG	EOA, cm^2
Starr-Edwards 9a-23mm	30	1.2
Bjork-Shiley 19mm	16	1.06
21mm	24	1.3
St Jude 19mm	16	1.2
21mm	6	2.7
Hancock(modified orifice)21mm	10	1.6
Carpentier-Edwards 21-23mm	13	1.1
Ionescu-Shiley 19mm	8	1.1
21mm	8	1.4

Abbreviations: PSG = peak systolic gradient
EOA = effective orifice area

(Table 2, Chest 85 : 391, 1984)

It is noted that the long term survival is not significantly different in the large series with the currently used devices (Bjork 1979, Craver 1981, Teply 1981, Ionescu 1982, Pelletier 1982).

Prospective studies evaluating long term survival of medical and surgical management of patients with severe aortic regurgitation

are not considered ethical and thus a retrospective analysis appears to be the only approach. Munoz (1975) failed to document a significant difference in 5 year survival between surgically and medically treated patients. Schwarz (1982), in evaluating the follow-up data of all patients with isolated chronic aortic valve disease who were recommended surgery between October 1975 and April 1980 (252 operated and 47 unoperated patients), showed that surgery did not influence survival in patients with aortic regurgitation and normal left ventricular function. Those with left ventricular dysfunction tended to live longer following surgery. Although this supports the practice of delaying aortic valve replacement, it does not allow negative conclusions regarding the effectiveness of valve replacement in aortic regurgitation as survival was the only criterion tested. In contrast, the Mayo Clinic experience of the medical and surgical long term follow-up (10-21 years) of 295 patients with Class III and IV chronic aortic regurgitation (McGoon 1981) showed that the 10 year survival was 4% in the medical treated group versus 45% in the surgically treated group. The survival in this group decreased to 38% by 19 years which equalled that of the control age and sex matched general population. Thus there was a significant improvement in survival in the operated group at 10 years with a minimal attrition rate thereafter. They speculated that earlier surgery might decrease the high early mortality.

II.6.2 Equilibrium Radionuclide Angiocardiography at Rest and during Exercise:

Ejection phase indices are presently widely used to assess pre- and postoperative ventricular function in patients with valvular heart

disease. Equilibrium radionuclide angiocardiography (ERNA) permits this to be done, not only non-invasively, but also during exercise, which may uncover dysfunction not evident during evaluation at rest. In the evaluation of 16 symptomatic patients who underwent aortic valve replacement between 1976 and 1977 and who were re-evaluated 6-9 months postoperatively, Borer (1979) found that although 63% of the patients had a normal resting ejection fraction pre-operatively, none had a normal functional reserve, with a mean ejection fraction at peak supine bicycle exercise of 37 $\pm$ 4%. Postoperatively resting ejection fraction normalised in a total of 14 of 16 patients. In contrast, only 4 had a normal peak exercise ejection fraction, i.e. aortic valve replacement can improve but does not usually normalise postoperative left ventricular systolic function during exercise; if exercise ejection fraction normalises, it does so in patients with a normal resting pre-operative ejection fraction. However, if pre-operative exercise ejection fraction was $<$ 35%, it did not normalise irrespective of the pre-operative resting value.

This study is in agreement with a small clinical and haemodynamic study following aortic valve replacement which reported that despite clinical and haemodynamic improvement at rest, cardiac output response to exercise remained subnormal(Bristow 1964). The small but significant improvement in resting ejection fraction after operation is in contrast to reports by other investigators that abnormalities in left ventricular function noted before operation most often persist to some degree after operation (Kennedy 1977, Bonow 1978, Rahimtoola 1978). This discrepancy appears to be related to earlier surgery, i.e. less impaired

functional class and preserved left ventricular systolic function.

Other findings from this study include (Borer 1979):-

(i) pre- and postoperative left ventricular function at rest or on exercise could not be accurately predicted from the pre-operative symptomatic status,

(ii) in addition, cardio-thoracic ratio on chest radiograph and the degree of left ventricular hypertrophy as estimated from the Romhilt-Estes electrocardiograph score (Romhilt 1968), were poor predictors of postoperative rest and exercise systolic function.

These findings suggested that irreversible myocardial dysfunction has often occurred by the time patients developed symptoms (Hirshfeld 1974, Bonow 1978), and only become apparent when the heart was stressed. Pre-operative irreversible myocardial damage secondary to chronic volume overload has been proven ultrastructurally with the demonstration of fibre degeneration, replacement fibrosis and altered myocardial architecture with fibre slippage due to excessive left ventricular distention (Ross 1971, Maron 1975).

II.6.3 Postoperative Echocardiographic Evaluation:

To determine whether volume overload myocardial hypertrophy secondary to chronic aortic regurgitation was reversible, the time course of change in left ventricular volume, mass and systolic performance was examined by Gaasch (1978). Pre-operative, early postoperative (7-10 days) and serial late postoperative echocardiograms were performed at 3, 6, 9, 12 and 24 months and are

summarised in figure 2.12 below. Due to the postoperative problem of paradoxical septal motion, Gaasch calculated the fractional increase in wall thickness from end-diastole to end-systole and used this measure as an index of left ventricular systolic function.

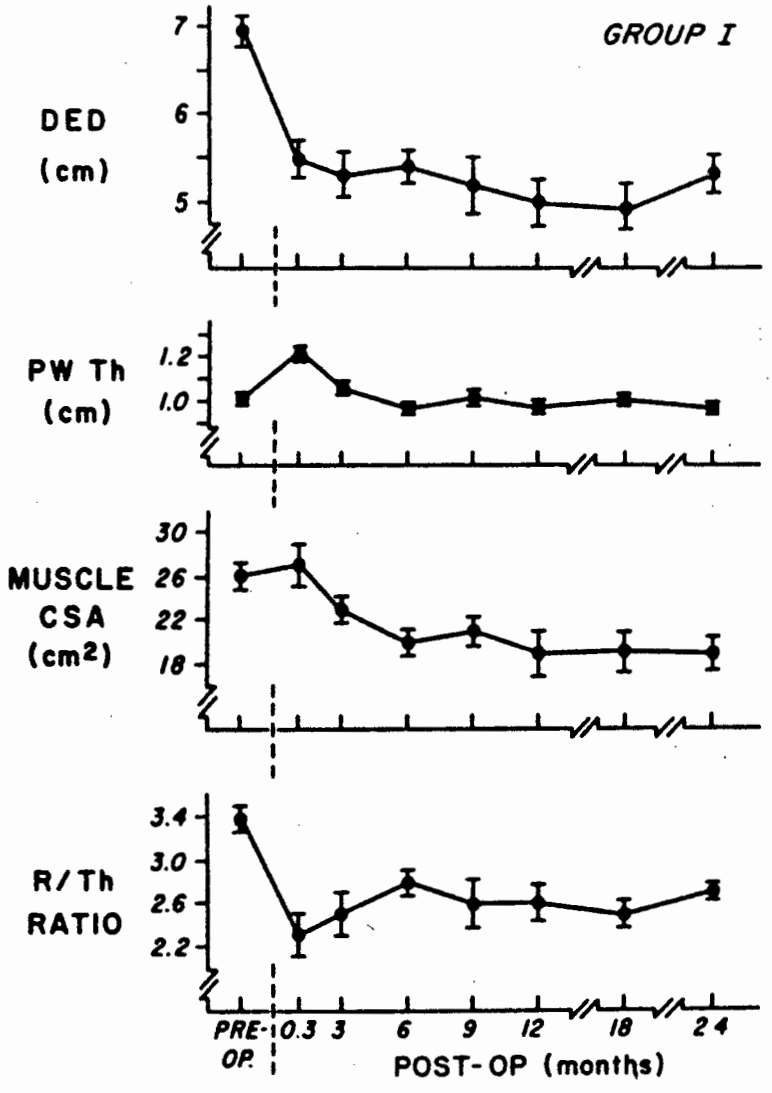
The left ventricular end-diastolic dimension decreased significantly early postoperatively, with a tendency for continued reduction in DED for the first 9 months postoperatively. The total decrease in volume ranged from 50% to 60%, with 75% of the overall decrease occurring in the first 7 to 10 days and predominantly determined by the degree of pre-operative regurgitation.

The lack of early change in muscle cross-sectional area (as a measure of left ventricular mass) despite a substantial reduction in left ventricular volume occurred as a result of a significant increase in posterior wall thickness. There was a progressive decrease in cross-sectional area ($\pm$ 23%) until 9 months, which corresponded to a 40% decrease in left ventricular mass or an absolute reduction of 100 grams of left ventricular muscle (Modified Troy method, 1972). This index was developed by Sasayama et al and was initially utilised in studies of the response of the left ventricle to chronic pressure overload. (Sasayama 1976).

These changes in left ventricular volume and mass are similar to other experimental (Papadimitriou 1974) and clinical studies (Burggraf 1975, Schuler 1976, Kennedy 1977). The change in left ventricular mass depends on the accurate determination of wall thickness and assumes that left ventricular myocardial hypertrophy occurs in a uniform manner and is accurately represented by free

wall thickness - this has been previously validated in patients with acquired valvular heart disease (Rackley 1964, Kennedy 1967).

Figure 2.12 SERIAL PRE-OPERATIVE AND POSTOPERATIVE ECHOCARDIOGRAPHIC DATA



(Figure 2, Circulation 58: 830, 1978)

The fractional shortening was not calculated postoperatively because of paradoxical septal motion. Pre-operative values were in the normal range and postoperatively the fractional increase in

wall thickness was used as a measure of left ventricular systolic function. Although there was a tendency to increase in the late postoperative studies, the changes were not statistically significant. This observation was also made by Schuler (1976) but other workers using both echocardiographic fractional shortening and angiographic ejection fraction have found little change (Papidimitriou 1974, Clark 1975, Kennedy 1977). Although there is a good correlation between fractional shortening and fractional increase in wall thickness, its wide range of normal (52 ± 30%), and its afterload dependency (Quinones 1978), limit its applicability in man.

The relation between muscle mass and ventricular volume, expressed as the ratio of internal radius to wall thickness (R/Th), tends to remain within the normal range in patients with chronic, compensated left ventricular volume overload. Once this ratio increases, it implies that LV dilatation has increased without adequate compensatory hypertrophy taking place.

Although easily measured directly from the echocardiogram and linearly related to the volume to mass ratio over a wide range of ventricular dimensions, certain qualifications are necessary before its prognostic significance in aortic regurgitation can be evaluated, viz. (i) acute aortic regurgitation must be excluded, (ii) radius to wall thickness ratio must be "normalised" for left ventricular systolic pressure so as to provide an index of peak systolic stress (radius to wall thickness ratio at end-diastole is nearly equal to this ratio at the time of peak systolic stress) (Grant 1965).

In 19 patients evaluated by Gaasch (1978), 4 had persistent postoperative left ventricular dilatation in the abscence of aortic regurgitation - the single pre-operative echocardiographic parameter that identified this group was a radius to wall thickness ratio of greater than 4. They thus concluded that left ventricular hypertrophy is not only a critical compensatory mechanism normalising wall stress, but insufficient muscle mass relative to chamber size implies a poor prognosis.

II.6.4 Postoperative Haemodynamic Assessment:

The response of the normal left ventricle to supine exercise consists of a small increase in stroke volume (Chapman 1960, Wang 1960) and a slight fall or rise of less than 3mmHg in left ventricular end-diastolic pressure (Braunwald 1963, Ross 1966). It it well established both experimentally (Sarnoff 1954) and clinically (Braunwald 1964, Ross 1964) that the failing left ventricle responds to a change in end-diastolic pressure or volume by an abnormally small alteration in stroke volume. These changes would not be apparent from changes in cardiac output and O_2 consumption alone, which may be adequate to meet the stress of exercise.

In explaining an abnormal rise in end-diastolic pressure (EDP) on exercise, several pertinent experimental and clinical observations need to be considered:-

(i) alterations in sympathetic tone and changes in heart rate, short of marked tachycardia, do not result in acute changes in the distensibility of the left ventricle (Mitchell 1960, Braunwald 1960, Sonnenblick 1963).

(ii) mean intrapleural pressure may decrease slightly during the hyperventilation that accompanies exercise (Donald 1955) and this effect would tend to lower the left ventricular EDP with reference to an external zero reference point.

Therefore, an increase in left ventricular EDP during exercise reflects an increase in end-diastolic volume, but during chronic volume overload, increased wall stiffness may magnify this pressure elevation (Braunwald 1963, Kennedy 1977). Grossman et al (Grossman 1974) however, in a combined echocardiographic and angiographic study evaluating late diastolic wall stiffness in patients with pressure and volume overload, found increased diastolic wall stiffness associated with pressure overload, but elevated stiffness in volume overload, when corrected for left ventricular dilatation, was similar to controls. They concluded that changes in EDP are secondary to alteration in end-diastolic volume and not to changes in the diastolic properties of the ventricular myocardium.

In patients with aortic regurgitation, regurgitant flow is promptly stopped by valve replacement. The prosthetic aortic valve thus functions as a competent but slightly stenotic valve under conditions of rest and moderate exercise, and the residual obstruction should be well within the capacity of the normal left ventricular myocardium. However, it could constitute a significant load in patients with left ventricular dysfunction (Beck 1966).

Contrary to the high incidence of abnormal cardiac function reported by Linhart (1967), numerous investigators have reported a 20% incidence of abnormal rest and exercise haemodynamics approximately nine months after aortic valve replacement (Bristow

1964, Beck 1966, Lewis 1966, Ross 1966, Bjork 1967). In a study by Hultgren et al (1969), eleven of nineteen patients with symptomatic class II to IV aortic regurgitation were re-evaluated a mean of 8.5 months after aortic valve replacement with a Starr-Edwards ball-valve prosthesis. Ten of the eleven cases were asymptomatic. The mean pulmonary capillary wedge pressure (PCWP) at rest pre-operatively was 15mmHg and dropped to 7mmHg postoperatively. Mean exercise PCWP dropped from 21mmHg to 10mmHg with only one patient having an exercise PCWP > 15mmHg. Although resting cardiac index rose from a mean of 2.68L/min/m^2 pre-operatively to a mean of 3.26L/min/m^2 postoperatively, exercise cardiac index was similar (4.67 vs 4.95). They thus demonstrated excellent haemodynamic improvement with normalisation of exercise PCWP in ten of eleven patients.

II.7.0 PROBLEMS ASSOCIATED WITH THE PUBLISHED DATA:

In evaluating the role of aortic valve replacement in asymptomatic severe aortic regurgitation, one must weigh up the results of operative versus non-operative therapy for severe aortic regurgitation from the published literature and come to a reasonably firm conclusion as to whether valve replacement therapy is indicated. Unfortunately, problems associated with the published data preclude such a comparison. These have been eloquently summarised by Rahimtoola (1983) and include:-

(i) Patients with mixed aortic valve disease or aortic stenosis are frequently not separated from those patients with isolated aortic regurgitation.

(ii) Criteria for the assessment of the severity of the lesion

are often not stated.

(iii) In some studies quantitative left ventricular functional data is not quoted although it may have been obtained.

(iv) The number of patients excluded in the analysis of results needs to be carefully scrutinised as the statistics on operative mortality, peri-operative myocardial infarction rate, anticoagulant haemorrhage and prosthetic valve endocarditis are significantly influenced by patients excluded from the analysis. Hospital mortality must be included to get a realistic idea of overall survival.

(v) Life table analysis is not always performed.

(vi) If life table analysis is performed, standard error (or confidence limits) should be presented because the precision of the estimated mean is directly affected by the sample size used to determine the mean. In some cases, so-called event-free curves include some complications.

(vii) The accurate evaluation of prosthetic failure or valve related complications can be extremely difficult. Patients with prosthetic valve malfunction may be asymptomatic and the non-invasive detection of mechanical prosthesis failure is unreliable. Thus some patients may have a degree of asymptomatic regurgitation or stenosis postoperatively which may influence left ventricular function. In addition, not all symptoms or bleeding complications are volunteered and published results thus probably report the minimum incidence of complications.

CHAPTER III

EXERCISE EVALUATION IN SEVERE AORTIC REGURGITATION

III.0.0 INTRODUCTION

Rushmer et al (1959) noted that deficiencies in our basic understanding of accepted haemodynamic theories are often corrected with the introduction of new or improved techniques. This observation, made more than 2 decades ago in an article about the ventricular response to exercise in animal preparations, remains applicable. In 1977, Borer et al, demonstrated exercise-induced abnormalities of left ventricular function not apparent at rest in patients with coronary artery disease. In symptomatic patients with severe chronic aortic regurgitation it is well known that various measures of left ventricular function including ejection fraction, end-diastolic pressure and cardiac output may be normal at rest, but that dysfunction almost invariably develops during exercise (Lewis 1970). Similarly, even asymptomatic patients may develop functional abnormalities when the heart is subjected to stress (Bolen 1976).

Thus it appeared that the sequential use of non-invasive ERNA for the assessment of left ventricular function during exercise might prove valuable in the follow-up of these patients before the development of symptoms or the occurrence of left ventricular dysfunction at rest.

Exercise evaluation will be discussed under the following headings:-

III.1.0 Pathophysiologic Principles.

III.2.0 Effects of Posture.

III.3.0 Type of Exercise.

III.4.0 Rest and Exercise Haemodynamics.

III.5.0 Radionuclide Left Ventricular Ejection Fraction.

III.1.0 PATHOPHYSIOLOGIC PRINCIPLES

The haemodynamic burden of alterations in preload, afterload and aortic impedance may alter the ventricular contraction pattern seen on an angiogram without necessarily representing a change in the intrinsic contractile performance of the ventricle (Mason 1973, Kreulen 1975).

Preload is the extent of stress on the muscle or filling of the ventricle at end-diastole which is measured clinically by end-diastolic volume or end-diastolic pressure. By the Starling principal, the greater the preload, the greater the shortening or ejection, given a constant afterload and contractile state (Little 1982).

Afterload is a more complicated concept, representing the tension against which the muscle contracts or ejects and is measured clinically as the peak systolic wall stress. Variables such as systolic pressure and ventricular size affect afterload.

Aortic regurgitation represents an increase in both preload and afterload with the net effect on the contraction of the ventricle depending on the relative contribution of each factor. Furthermore, compensatory hypertrophy alters contractility and may affect the extent of ventricular emptying seen on the angiogram.

Just as the chronic haemodynamic burden of severe aortic regurgitation may alter ventricular contraction, so does its removal by aortic valve replacement. With the removal of the regurgitant volume following valve replacement, there is usually an immediate decrease in end-diastolic volume with little or no change in end-systolic volume and thus a resultant decrease in ejection fraction. This reduction is primarily due to a change in loading conditions and not to a decrease in contractility. With time end-systolic volume continues to decrease and the ejection fraction improves in most patients.

III.2.0 THE EFFECTS OF POSTURE

Posture has important physiologic effects on the cardiovascular system both at rest and during exercise (Crawford 1979). Recent studies have reported significant differences in the haemodynamic and functional responses to exercise with alterations in posture in normal persons (Poliner 1980, Manyari 1983) and in patients with coronary artery disease (Thadani 1977, Freeman 1981). These effects of posture on exercise response should be especially relevant in patients with aortic regurgitation because of the altered loading conditions and the dynamic nature of the leak in individual patients.

Shen et al (1985) utilising equilibrium radionuclide angiocardiography demonstrated that posture was important in determining left ventricular response to exercise in patients with moderate to severe aortic regurgitation. Its effects on haemodynamics included a higher resting heart rate and a lower left ventricular stroke volume in the upright posture. The former may be the result

of increased sympathetic and reduced vagal tone (Gauer 1965), the latter because of the decreased left ventricular preload. During exercise, stroke volume remained unchanged in the supine position and slightly increased in the upright position.

In contrast to normal subjects where left ventricular ejection fraction was similar at rest in both postures, ejection fraction was significantly lower in the upright position in patients with aortic regurgitation and this may be a function of reduced preload without a compensatory increase in contractility (Poliner 1980, Manyari 1983). During exercise left ventricular ejection fraction decreased in the supine position and was unchanged in the upright posture. It was proposed that the results obtained in one body position should not be compared to those in another in the individual patient and since exercise-induced left ventricular dysfunction occurs more frequently in the supine posture, this may be the preferred position for assessment of left ventricular functional capacity in asymptomatic patients with aortic regurgitation. Several other studies have been reported and will be discussed.

III.3.0 EXERCISE TYPE

Left ventricular functional reserve can be assessed non-invasively by equilibrium radionuclide angiography used in conjunction with a number of provocations, including dynamic bicycle exercise, isometric handgrip exercise, and cold pressor stress testing.

III.3.1 Isotonic Bicycle Exercise

Although isotonic bicycle exercise is the most commonly employed

means of stress, some workers believe that isometric handgrip exercise is a more "physiologic approach" to the evaluation of left ventricular functional reserve.

Dynamic exercise increases myocardial oxygen demand primarily by a sympathetic mediated increase in heart rate and contractility without a significant increase in left ventricular diastolic pressure.

III.3.2 Isometric Hangrip Exercise

During handgrip exercise, there is little increase in heart rate but a significant increase in systemic pressure, most likely caused by impedance to the increased forearm blood flow by sustained muscle contraction (Savin 1980). In normal subjects, despite this increase in afterload, there is no increase in left ventricular end-diastolic pressure but in patients with aortic regurgitation, left ventricular end-diastolic pressure increases and stroke work decreases (Helfant 1971, Kivowitz 1971, Osbakken 1981).

In patients with chronic aortic regurgitation, left ventricular dysfunction results from a progressive increase in both preload and afterload. Once preload has been exhausted, it has been postulated that a further increase in afterload results in a deterioration in left ventricular function (Ricci 1982). Handgrip exercise which represents an afterload stress, has been used as a simple provocative non-invasive test to assess the severity of impairment of left ventricular functional reserve. In addition, its effects disappear within a few seconds of release and it has been postulated that it is a better provocative test in patients with aortic regurgitation than dynamic bicycle exercise because of its

potential ability to evoke a greater increase in left ventricular end-diastolic pressure.

However, a number of disadvantages of this manoeuvre preclude its general use and these include:-

(a) Poor patient co-operation with relatively submaximal handgrip resulting in minimal stress to the circulation. This can be offset by taking a rise in systolic blood pressure of 15-20mmHg as a measure of the adequacy of the stress, similar to the increase in heart rate during isotonic exercise (Ellestad 1969),

(b) An arrhythmogenic effect (Athins 1971) and

(c) The performance of the Valsalva manoeuvre during the test. This can be avoided by simple patient instruction and careful observation by the attending physician during the sustained three minute contraction (Gorlin 1957).

III.4.0 REST AND EXERCISE HAEMODYNAMICS

It is well known that impairment of cardiac function often does not result in distinct haemodynamic abnormalities at rest. It frequently is necessary to determine the circulatory response during exercise before any functional limitation can be demonstrated. In addition, alterations in posture significantly alter the haemodynamic profile, with the resting values for end-diastolic pressure, pulmonary capillary wedge pressure, cardiac index, stroke volume index and stroke work index being significantly lower in the erect position and heart rate being higher (Wang 1960, Bevegard 1963, Tuckman 1966).

The increased venous return and consequent increased cardiac output is the major mechanism by which the elevated metabolic requirements of the exercising muscle are satisfied during exercise. Cardiac output increases as a linear function of oxygen consumption (Bevegard 1963) and can rise up to four fold in man (Saltin 1968), with heart rate being the predominant mechanism under physiologic conditions. Since the classic work of Starling (1920), stroke volume has been asigned a pre-eminent role in mediating an increase in cardiac output during exercise, particularly during near maximal exercise (Horowitz 1972). At low or moderate levels of supine exercise the heart rate increases to augment the cardiac output, whereas at maximal exercise, there is also an increase in end-diastolic volume and stroke volume. Furthermore, in the supine position, with the leg lifting necessary to perform exercise studies, there is a slight increase in end-diastolic volume above the control measurements with the legs in the supine position. Therefore, further changes in end-diastolic volume during supine exercise may not be apparent. On the other hand, blood pooling reduces the end-diastolic volume at rest in the upright position. During upright exercise, the end-diastolic volume increases but may remain lower than the end-diastolic volume at peak supine exercise.

Numerous studies in the supine position have confirmed that in the absence of severe pulmonary hypertension or obstruction at the level of the pulmonary veins or left atrium, the mean pulmonary capillary wedge pressure corresponds approximately to the left atrial pressure, which itself is approximately equal to the diastolic pressure in the left ventricle (Luchsenger 1962, Thadani 1977). During exercise there is an increase in pulmonary capillary

wedge pressure during both postures but in normal subjects exercise pulmonary capillary wedge pressure does not exceed 15mmHg.

Lewis and co-workers (1970) using a one-legged bicycle ergometer, reported that the classic clinical criteria for judging the severity of aortic regurgitation were of little value in predicting the exercise haemodynamics in 23 patients with Class II or III chronic aortic regurgitation. Although resting cardiac index was normal in most patients, it rose insufficiently with exercise in 11 cases. Paradoxically, they found that the 12 patients with an appropriate cardiac index response had elevated left ventricular end-diastolic pressures, while those with a low cardiac index usually had normal pressures. No obvious explanation was offered.

In an attempt to better understand the ejection fraction response during exercise in aortic regurgitation, Boucher et al (1983), in a study of 28 asymptomatic or minimally symptomatic patients with catheter proven severe aortic regurgitation, used supine symptom-limited bicycle exercise and stratified patients on the basis of their pulmonary capillary wedge pressure response to exercise. This objective measure was then used to compare the clinical, respiratory gas exchange and haemodynamic data in the two groups. An exercise pulmonary capillary wedge pressure of 15mmHg was used to divide patients into normal and abnormal left ventricular function (Ross 1966, Braunwald 1969, Rahimtoola 1975). Although 75% of patients had normal resting pulmonary capillary wedge pressures, only 40% were normal at peak exercise. Using stepwise multiple regression analysis, the best predictor of the exercise pulmonary capillary wedge pressure was the oxygen uptake at peak

exercise. This measure reflects the integrity of the cardiovascular system in terms of its ability to adequately deliver oxygen to the working muscles (Wasserman 1975, Astrand 1976). Its primary determinants are central cardiac output, the ability to shift regional cardiac output to the working muscles and peripheral oxygen extraction. Mechanisms for reduced uptake include relatively reduced forward cardiac output, reflex vasoconstriction or the inability to vasodilate - this may translate in patients with poor cardiac compensation as an increased pulmonary capillary wedge pressure (Vatner 1976). Failure to shift regional cardiac output to working muscles may occur independently of a reduction in central cardiac output, and may explain the better correlation of peak oxygen uptake with pulmonary capillary wedge pressure, rather than ejection fraction. The exercise level achieved is an alternative method of approximating peak oxygen uptake.

When peak oxygen uptake was excluded, other variables also correlated, including absolute rest and exercise ejection fraction and age, but not change in ejection fraction on exercise. Numerous reasons could explain the inability of change in ejection fraction on exercise to correlate with filling pressures, namely, interpatient variability in the degree of change in exercise preload, afterload and contractile stimulation, altered loading conditions due to a decrease in regurgitant volume (Levinson 1970) and other independent causes of wedge pressure elevation, e.g. diastolic stiffness (Eichorn 1982) or exercise induced mitral regurgitation.

Age was the only clinical variable that correlated with the exercise pulmonary capillary wedge pressure by multiple regression analysis. This was similar to other reports (Schuler 1982, Gerstenblith 1976) where age-related abnormalities in cardiac contraction, ventricular relaxation and peripheral resistance occurred in some patients, and thus impaired the ability of older patients to tolerate severe aortic regurgitation. Although this objective measure of exercise pulmonary capillary wedge pressure defined a subset of patients with asymptomatic severe aortic regurgitation and left ventricular dysfunction, its prognostic value in terms of the development of severe symptoms, irreversible left ventricular dysfunction or death are presently unknown.

III.5.0 RADIONUCLIDE LEFT VENTRICULAR EJECTION FRACTION

Ejection fraction, the ratio of stroke volume to end-diastolic volume, is a simple, meaningful, unitless, non-invasive measure of cardiac function, but does not measure contractility (Krayenbuehl 1968). It is significantly influenced by altered loading conditions and other factors including age, sex, resting heart rate, ejection fraction at rest, level and type of exercise (Borer 1979, Port 1980, Jones 1981). In addition, left ventricular performance during exercise may be modified by training (Rerych 1980, Bar-Shlomo 1982). Exercise (dynamic and isometric) equilibrium radionuclide angiography (ERNA) was first proposed by Borer and co-workers (1978, 1979) as a method of unmasking systolic ventricular dysfunction not evident at rest. The equilibrium technique is the most widely used method (Berger 1981). The normal reported response is a 5% or greater increase in ejection

fraction from rest to peak exercise although subjects with a resting ejection fraction of greater than 70% may not increase their ejection fraction with exercise (Thadani 1978, Osbakken 1983).

Borer and co-workers found that all 21 symptomatic and 16 of 22 asymptomatic patients with severe aortic regurgitation had an abnormal supine exercise left ventricular ejection fraction increase of less than 5%. The presence of an abnormal exercise ejection fraction response was unrelated to symptoms, degree of left ventricular hypertrophy on ECG or increased cardio-thoracic ratio on chest X-ray. The authors suggested that the unmasking of exercise induced left ventricular dysfunction might indicate that surgery was necessary, but because of the large number of asymptomatic patients in this category it may be overly sensitive. In addition, motivation and individual differences in the way patients change heart rate, preload, afterload and sympathetic status may all affect ejection fraction in different ways (Wasserman 1975, Astrand 1976, Port 1980). Posture during exercise (supine versus erect) may also affect the ejection fraction (Marx 1982, Manyari 1982). Numerous factors influence the ejection fraction response to exercise and preclude its use in establishing a simple criterion to answer questions such as "what is the optimal time to perform aortic valve replacement in patients with asymptomatic severe aortic regurgitation?"

In an attempt to better understand the left ventricular ejection fraction response in patients with severe aortic regurgitation, Boucher et al (1982) correlated left ventricular ejection fraction and left ventricular end-diastolic pressure during supine exercise

in 28 symptomatic or minimally symptomatic patients. Only 40% (8 patients) had a normal exercise pulmonary capillary wedge pressure response and these patients had a higher rest (64% ± 8%) and exercise (63% ± 1%) ejection fraction compared to the 12 patients with higher filling pressures (rest 49% ± 13%; exercise 4% ± 18%, P <0.01). Although the difference in mean ejection fraction between the two groups was significant, overlap did occur. The best correlate with exercise pulmonary capillary wedge pressure was peak oxygen uptake, and although rest and exercise ejection fraction values also demonstrated a correlation, the change in ejection fraction with exercise and the cardio-thoracic ratio did not correlate. They concluded that in asymptomatic patients with aortic regurgitation the ejection fraction did not reflect left ventricular reserve and the spectrum of haemodynamic findings was large and varied.

These apparently paradoxical observations may be partly explained by a number of limitations of this measure in assessing left ventricular performance in aortic regurgitation. The haemodynamic burden of volume overload in aortic regurgitation is complex (Ross 1974, Ricci 1980). In addition, the regurgitant volume decreases with exercise because of reduced diastolic filling time and an exercise induced decrease in peripheral vascular resistance (Levinson 1970). Thus the forward stroke volume actually increases despite a fall in total stroke volume and end-diastolic volume. Because the ejection fraction reflects total stroke volume and does not separate regurgitant from forward stroke volume, it is possible to have a drop in ejection fraction with an increase in forward stroke volume during exercise.

For these reasons, the exercise response of ejection fraction in patients with chronic aortic regurgitation is likely to be different from that in normal patients, and it may be inappropriate to compare the ejection fraction during exercise in chronic aortic regurgitation with the expected response of the normal left ventricle.

As previously discussed, the position of the patient during bicycle exercise is also an important factor. Several studies have used upright exercise, with Iskandrian and associates (1981) and Lewis (1982) reporting a 5% or more increase in ejection fraction during exercise in the majority of asymptomatic patients and also symptomatic patients. However, the sample size of symptomatic patients was small. Marx and co-workers (1982) used both supine and upright exercise in a small study of 12 patients with aortic regurgitation. The ejection fraction was similar at rest, but the change in ejection fraction was higher for upright than supine exercise. Only two of the 12 patients studied had a fall in ejection fraction of 5% or greater during upright exercise, compared with 8 of 12 patients during supine exercise. Therefore, ejection fraction response in one position during exercise should not be applied to another.

Other parameters utilising radionuclide ventriculography have also been studied, including left ventricular ejection rate (Johnson 1982), volume changes during supine exercise (Dehmer 1981), and the end-systolic pressure-to-volume relationship as an assessment of myocardial contractility (Schuler 1982). This ratio has been proposed as an alternative to exercise evaluation.

Bonow and co-workers (1980) studied 45 asymptomatic patients with aortic regurgitation by echocardiography, exercise ERNA and treadmill testing (see Table 2.3).

Twenty seven patients (Group A) did not complete 22.5min of the National Institute of Health exercise treadmill protocol without developing symptoms, whereas 18 patients (Group B) did. Groups A and B did not differ with respect to rest and exercise ejection fraction, end-systolic dimension or fractional shortening, yet the survival rate amongst 32 patients undergoing aortic valve replacement was 100% in Group B, but 53% in Group A. These findings challenge the prognostic significance after aortic valve replacement of the considered markers of left ventricular dysfunction, with exercise duration alone appearing to have predictive value.

Ultimately the best method of determining which pre-operative parameter identifies the patient with severe aortic regurgitation at risk of irreversible left ventricular dysfunction, is to analyse patients after aortic valve replacement. Previous studies, including one from our institution (Forman 1980), have shown that a normal resting pre-operative left ventricular ejection fraction is associated with an excellent prognosis. Similarly another study shows that these patients have normal ejection fraction late after valve replacement (Merci 1981). Only patients with a reduced pre-operative ejection fraction at rest have an increased postoperative morbidity and mortality, and even in this group, the majority normalise their resting ejection fraction (Clark 1980). In contrast in a radionuclide and cine-angiographic study of 16

symptomatic patients with aortic regurgitation before and six months postoperatively, Borer et al (1979) reported that resting left ventricular ejection fraction normalised postoperatively (46 ± 3 to 57 ± 4%) but that although exercise ejection fraction improved (37 ± 4 to 53 ± 4%), it did not normalise following aortic valve replacement.

Thus in conclusion, although exercise equilibrium radionuclide angiography appears to provide an assessment of left ventricular function, its role in aiding the timing of aortic valve replacement is not clearly defined.

CHAPTER IV

THE DEVELOPMENT AND REGRESSION OF LEFT VENTRICULAR HYPERTROPHY

IV.0.0 INTRODUCTION

A discussion of the development and regression of left ventricular hypertrophy is pertinent as hypertrophy is an important factor in the structural adaptation of heart muscle, and regression of ventricular hypertrophy is vital to the structural and functional normalisation of heart muscle following surgical correction of valvular lesions that result in left ventricular hypertrophy (Meerson 1977).

Pathologically, cardiac hypertrophy is defined as a heart mass exceeding the accepted limits of normal for age, sex and body weight (average 295G for adult men and 250G for adult women). Traditionally it has meant that the increase in the mass of the heart is a consequence of an increase in the size of its constituent cells. However, although hypertrophy is mainly due to enlargement of individual muscle cells, this is an oversimplification, as an increase in the number of various connective tissue proteins in the interstitial space also occurs (Ferrans 1984). The connective tissue component may have important but as yet not clearly defined effects on systolic and perhaps more importantly diastolic function.

Evidence supports the concept that normal cardiac growth and hypertrophy develop in response to increased haemodynamic loading and abnormal systolic and diastolic stresses at the myocardial

fibre level and the pattern of hypertrophy reflects the nature of the inciting stress (Linzbach 1960, Grant 1965, Grossman 1975). It is not understood how the heart translates signals generated by haemodynamic activity (a physical phenomenon) into biochemical and ultrastructural changes (Zak 1984).

Chronic volume overload is initially matched by adequate hypertrophy in the appropriate pattern, but in some instances, when the process fails to keep pace with the haemodynamic burden, systolic wall stress rises, possibly converting physiologic to pathologic hypertrophy and eventually left ventricular pump failure ensues.

The development and regression of hypertrophy in the normal and failing heart will be reviewed under the following headings:-

IV.1.0 Biochemical, physiological and ultrastructural aspects of cardiac hypertrophy.

IV.2.0 Pathophysiologic mechanism.

IV.3.0 Detection.

IV.4.0 Clinical implications.

IV.5.0 Regression - clinical importance and longterm prognostic implications.

IV.1.0 BIOCHEMICAL, PHYSIOLOGICAL AND ULTRASTRUCTURAL ASPECTS:

Shortly after birth the myocardial muscle fibre loses mitotic activity and myocardial cell enlargement is the principal process by which the heart hypertrophies. Muscle mass increases with workload (Zak 1973, Wikman-Coffelt 1976) and the heart physiologically responds to an increased workload by increasing the number of sarcomeres. Although the mechanism of sarcomere genesis

has not been fully elucidated, two micro-anatomical locations for new sarcomere production have been suggested, namely the intercalated discs (Adomian 1974) and the Z bands (Legato 1970).

Pressure alone (Schreiber 1978), or simply stretch of muscle fibres (Vandenburgh 1979) appears to activate the genetic apparatus of the myocardial cell with resultant enhanced nucleic acid (Fanburg 1968, Morkin 1968), and protein, including myosin, synthesis (Schreiber 1966, Zak 1976). It is suggested, but as yet not generally accepted, that new genetic expression in the form of new myosin isoenzymes (Schwartz 1978, Flink 1979) occurs. Haemodynamic overload is followed within a very short space of time by increased protein synthesis with the preferential synthesis and accumulation of mitochondrial proteins during the early phases of myocardial hypertrophy (Albin 1973, Zak 1976). Although mitochondria increase both in size and number with the progression of hypertrophy (Schreiber 1973), the normal inciting stimulus of mitochondrial neogenesis is not established at this time (Gevers 1972). Following these early microsomal and mitochondrial adjustments in response to wall stress, there is an increase in myosin biosynthesis. Protein degradation, however, remains constant (Everett 1977, Laurent 1978). These structural and biochemical changes that occur early in the genesis of cardiac hypertrophy may not be the same for physiological and pathological hypertrophy, and the asynchronous synthesis of certain cardiac proteins (e.g. a disproportionate synthesis of mitochondrial to myofibrillar proteins) may result in normal or supernormal velocity of muscle shortening in physiological hypertrophy and a depressed velocity of shortening in pathological hypertrophy (Wikman-Coffelt 1979).

With time, myocardial hypertrophy progresses and further structural and biochemical alterations occur:-

(i) enhanced myofibrillar accumulation results in a decrease in the relative volume occupied by the mitochondria in the cardiac fibre (Wollenberger 1966).

(ii) an increase in muscle mass and enlargement of individual muscle fibres (Geha 1966). The resultant decrease in the cell surface-to-cell volume ratio, may limit efficient exchange of metabolites and tissue gases and serve as a stimulus for collagen synthesis. The maximum fibre size attained with myocardial hypertrophy is restricted partially by the ability of component organelles to increase in number. The distance between capillaries also increases until the slower growth of the capillary bed "catches up" (Tomanek 1982). It is unclear whether a completely normal relationship of cell size to capillary density is ever regained.

The ability of mitochondria to increase in number proportionate to demands may determine whether the contractile units work at a decreased, normal, or increased shortening velocity, which in turn is partially regulated by the type of myosin isoenzyme present. There is a direct relationship between the rate of calcium-activated myosin ATPase activity and the maximum velocity of muscle shortening (Barany 1967). Animal studies have demonstrated that accompanying myocardial hypertrophy, new isoenzymes of myosin occur, principally determined by the degree of haemodynamic stress (Wikman-Coffelt 1975). In the case of physiological hypertrophy these new isoenzymes demonstrate an increased rate of ATP

hydrolysis (Flink 1977) and, in the case of pathological hypertrophy, a decreased rate of ATP hydrolysis (Schwartz 1978). The decrease in myosin ATPase activity in failing, haemodynamically stressed, hypertrophied hearts is associated with alterations in the sulfhydryl groups of myosin involved in the active site (Thomas 1977) and may be seen as a compensatory mechanism because the decreased shortening velocity leads to less heat production and a more efficient contraction. It is important to note however, that in man changes between the isoenzymes (V1 and V3) are considered not to be an important adaptive mechanism (Mercadier 1983) and the relevance of these changes to clinical events are as yet unclear.

When the stimulus to hypertrophy is particularly prolonged and intense, excessive cell growth is elicited with disproportionate biosynthesis of organelles and contractile proteins, thereby leading to the evolution of pathological hypertrophy. This form of hypertrophy is characterised by a reduced myosin ATPase activity (Wikman-Coffelt 1975, 1976), and depressed contractile function (Meerson 1969).

In summary, all inducers of hypertrophy appear to initiate the process by a common mechanical-biochemical coupling mechanism; the work overload causes an increased pressure on the myocardial cells with stretch of muscle fibres and this, perhaps mediated by noradrenaline release, causes an augmentation of RNA transcription and protein synthesis. Then, depending on the severity of the workload, secondary factors such as increased tissue pCO_2 could determine whether the heart adjusts to the new work demand by developing the characteristics of either physiological or pathological hypertrophy (Wikman-Coffelt 1979).

Histologically normal left ventricular muscle cells range up to 15μm in diameter. When hypertrophy occurs, the diameter of many cells exceed 20μm and cells with a diameter of 50μm may be seen, resulting in marked variation in the diameter of adjacent myocardial cells. The reason for such variation in cell size, presumably all subject to the same haemodynamic stress, is not certain.

While ultrastructural changes in the early and stable phases of hypertrophy reveal variations in the appearance of hypertrophied cardiac muscle cells depending on the cause and the stage of the hypertrophy, the size of the contractile elements are similar to normal cardiac muscle cells (Richter 1963). In the late stage of hypertrophy a variety of degenerative changes and interstitial fibrosis dominate the morphologic picture. The effects of these degenerative changes on measured systolic function are difficult to separate from the effects of hypertrophy alone. With removal of the haemodynamic load regression of hypertrophy may occur but restoration of normal architecture and function is unlikely if these degenerative changes are extensive.

The degenerative changes include (a) loss of contractile elements particularly the thick myosin filaments and specialised intercellular contacts; (b) alterations in other cytoplasmic organelles; and (c) interstitial fibrosis. The stimuli that produce hypertrophy of myocardial cells also stimulate the formation of collagen. Occasionally the rate of collagen synthesis is excessive and it is postulated that this may impair left ventricular mechanical function, particularly diastolic function. At a biochemical level, the increase of collagen can be measured by

an increase in hydroxyproline, the level of which remains unaltered when the inciting stimulus is removed (Cutiletta 1975). This is presumably because collagen deposition in the interstitial space makes it inaccessible to normal breakdown. This permanent increase in the content of left ventricular connective tissue may have important long term consequences, such as alterations in diastolic function of the left ventricle (Brutsaert 1985).

IV.2.0 PATHOPHYSIOLOGIC MECHANISM

Normal ventricular growth involves an increase in the number of myocardial cells (HYPERPLASIA) throughout foetal life and up to 6 months of age (Perloff 1982). The stimulus is predominantly haemodynamic with a possible hormonal or biochemical link (norepinephrine - Laks 1976). Thereafter cardiac growth is associated with progressive cell enlargement (HYPERTROPHY), resulting in a 20 times increase in mass (Zak 1973, Perloff 1982). Thus, substantial increases in ventricular dimension and wall thickness result from the addition of new contractile proteins in series and in parallel within a virtually constant population of cardiac muscle cells (Zak 1973, Wikman-Coffelt 1979). Normal growth is therefore a form of "physiologic" volume overload hypertrophy (Wikman-Coffelt 1979).

In patients with aortic regurgitation, Grant et al (1965) observed that the eccentric hypertrophy that develops strongly resembles the pattern of normal growth; in contrast, pressure overload or concentric hypertrophy involves a disproportionate increase in wall thickness at a normal or reduced chamber dimension.

In order to understand the relationship between inciting stimulus

and the pattern of hypertrophy, wall stress (the magnitude of forces acting at the myocardial cell level) needs to be calculated. A modification of the Law of LaPlace (Grossman 1975) is used, which states that the wall stress or tension per unit cross sectional area (WS) is proportional to the pressure (P) and radius (R) of the chamber and inversely proportional to its wall thickness (h) (Gaasch 1979):-

$$WS = \frac{P.R}{/h}$$

The following table 4.1 demonstrates the proposed hypothesis of Grossman (1980), invoking the relationship between inciting stimulus and pattern of hypertrophy.

Table 4.1 PATHOGENESIS OF HYPERTROPHY:

(Table 1, J Am Coll Cardiol 3: 1310, 1984)

When the primary stimulus to hypertrophy is pressure overload, increased left ventricular systolic pressure and wall stress result in the parallel addition of new myofibrils, with resultant increase in wall thickness and concentric hypertrophy. The wall thickening tends to normalise wall stress. In contrast, when volume overload is the inciting stimulus, increased diastolic pressure and wall

stress leads to the series addition of new sarcomeres, fibre elongation and chamber enlargement. This progressive chamber enlargement results in elevated systolic wall stress by the LaPlace relationship with the subsequent development of eccentric hypertrophy to normalise the systolic stress; i.e. myocardial hypertrophy occurs in concert with chamber dilatation and thereby serves to normalise the force per unit cross sectional area of the myocardium. This resembles the normal myocardial growth pattern in which the radius-to-wall thickness ratio (R/Th) remains constant (Gaasch 1979) and may account for the fact that patients with chronic volume overload may remain asymptomatic for many years despite severe volume overload and significant cardiac enlargement.

IV.3.0 DETECTION:

The electrocardiogram is commonly used for the detection of left ventricular hypertrophy. It has a specificity of 95%, however, its sensitivity is less than 60%. The Romhilt-Estes point score (Romhilt 1969) is better than the Sokolow-Lyon voltage criteria (Sokolow 1949) and the praecordial leads better than the limb leads (Reichek 1981). Carroll (1982) reported a strong correlation between left ventricular voltage on the electrocardiogram and muscle cross-sectional area on the echocardiogram in data from 59 studies before and after aortic valve replacement in patients with chronic aortic regurgitation ($r = 0.81$).

At present M-mode echocardiography is widely used for the detection of left ventricular hypertrophy, correlating well with autopsy left ventricular mass (Devereux 1980) and having a sensitivity and specificity in excess of 90%. There are a number of measurement methods which all assume that the ventricle is ellipsoidal at end-

diastole. Left ventricular mass is then calculated using a specific gravity of ventricular muscle of 1.05 G/cm^3 (McFarland 1978, Reichek 1981). However, there are limitations in using this technique to measure wall thickness and the calculation of left ventricular mass, namely:-

(i) difficulties in defining the endocardium - the Penn convention method which excludes endocardial echoes (compared to the standard convention method) provides a more accurate estimate of left ventricular mass.

(ii) the problem of abnormal echoes (e.g. chordal structures and left ventricular bands)(Keren 1984).

(iii) significant interobserver variation and difficulty in reproducibility (Felner 1980, Pietro 1981).

(iv) abnormal left ventricular geometry.

Two dimensional echocardiography is probably the method which is most widely available and most accurate at present and has been shown to correlate well in clinico-pathologic studies(Salcedo 1979, Helak 1981).

IV.4.0 CLINICAL IMPLICATIONS:

Although normal cardiac growth ("physiologic" volume overload) and volume overload hypertrophy in experimental animals is associated with normal contractile function (Turina 1969, Newman 1978), there appear to be a number of differences in patients with clinical volume overload:-

(i) The degree of hypertrophy is proportional to the duration and haemodynamic severity of the volume overload (Panidis 1984), the myocardium does not possess an unlimited ability

to increase its mass in response to haemodynamic stress. At present the limiting factor is not known, but may be capillary density and cell size (Tomanek 1982). The inability of hypertrophy to keep pace with the haemodynamic burden may lead to increased wall stress and an unfavourable outcome (Field 1973, Gaasch 1978, Benjamin 1981).

(ii) When severe left ventricular hypertrophy develops, some patients exhibit depressed systolic function and do not recover normal function after corrective surgery. There appears to be a pathologic continuum from normal to severely depressed contractile function in patients with volume overload due to chronic aortic regurgitation. Gaasch and co-workers (1978) postulated that this might be due to inadequate hypertrophy, with an inability to sustain the addition of new myofibrils in parallel to balance the series addition of new sarcomeres, resulting in a high wall stress with decreased fibre shortening and eventual ventricular failure. In addition, failure to improve ventricular performance postoperatively could reflect persistence of high wall stress (low h/R) secondary to:-

-inability to resorb new sarcomeres laid down in series (Jarmakani 1971).

-continued inability to increase fibre thickness by parallel addition of new myofibrils.

However, exactly when compensatory (adaptive) hypertrophy becomes "pathologic", irreversible myocardial damage and impaired contractility is presently unknown.

IV.5.0 REGRESSION AND ITS SIGNIFICANCE:

Although experimental and clinical data reveal regression of ventricular hypertrophy after correction of haemodynamic overload (Gault 1970, Cutiletta 1975, Carey 1970), contractility often remains depressed (Gault 1970), with connective tissue not appearing to regress as readily as myocardial mass (Cutiletta 1975). The extent of reversibility of contractility changes appear to depend on the inciting stimulus, duration of wall stress and the age, health and species concerned.

Many studies (Gaasch 1978, Schuler 1979, Carroll 1981, Carroll 1982), using echocardiographic or angiographic techniques, have shown regression of left ventricular hypertrophy and improvement in indices of myocardial contractility in most (but not all) patients 6 to 15 months after aortic valve replacement. However, in some patients with isolated aortic regurgitation, increased left ventricular mass and abnormal systolic function persist despite technically successful aortic valve replacement (Schwartz 1978, Pantely 1978).

Some reports (Boucher 1981, Toussaint 1981) show that even if performance is initially depressed postoperatively, it may improve with time.

Most of these studies are limited by the small number of patients in each study and the serial assessment by means of M-mode echocardiography with its inherent difficulties (Teicholz 1976, Ditchey 1981, Pietro 1981).

Experimentally Papadimitriou (1974) showed that regression of left ventricular mass after correction of volume overload was associated

with normalisation of myofibre ultrastructural morphology; however, the role of histopathologic myocardial changes in the regression of hypertrophy and the recovery of cardiac function after removal of volume overload in man has not been clearly defined (Jarmakani 1971, Dodge 1974) with contradictory reports in the more recent literature (Maron 1975, Maron 1975, Schwarz 1978). It is generally accepted that in advanced left ventricular hypertrophy interstitial fibrosis develops, probably as a result of focal cell destruction (Wigle 1957, Linzbach 1960, Reichenbach 1967), but this fibrosis has not been shown to be a primary determinant of impaired left ventricular function. (Maron 1975, Schwarz 1978).

In patients, regression of left ventricular mass is usually PARTIAL (Kennedy 1977, Bodem 1978, Carroll 1981) with the final estimates of mass remaining somewhat greater than normal. Varied explanations include irreversible fibrosis (Reichenbach 1967, Maron 1975) and relative prosthesis "stenosis" with the substitution of pressure overload for volume overload (Schuler 1979). Most importantly, regression may be a slow process which occurs late and thus may not be detected 6-9 months postoperatively when patients are usually re-evaluated.

It is not known whether the clinical and functional outcome is influenced by the extent of the regression. Much of the reported data on postoperative left ventricular function has not been serially obtained, and for this reason the time course of such changes has not been fully evaluated.

Carroll et al (1981) speculate that persistent left ventricular hypertrophy after aortic valve replacement may be associated with persistent dysfunction, while gradual regression parallels

functional improvement. In contrast, Henry et al (1980) and Schuler (1979) found no pre- or postoperative echocardiographic or haemodynamic variables that could predict irreversibility of hypertrophy, persistence of left ventricular dysfunction or ultimate prognosis.

Thus, regression of left ventricular hypertrophy does not necessarily assure normalisation of left ventricular function, and failure to regress does not mean that function is abnormal (Perloff 1982). Further studies are required to determine the degree and type of left ventricular hypertrophy that constitutes a "pathologic" irreversible state and to highlight the consequences of the regression of hypertrophy.

CHAPTER V

DIASTOLIC FUNCTION IN SEVERE AORTIC REGURGITATION

V.0.0. INTRODUCTION

Most investigations concerning ventricular function in valvular heart disease have examined systolic performance of the ventricle. However, the diastolic properties of the heart (its ability to relax) are also important, possibly independent factors that may precede or accompany the development of impaired systolic function (Bristow 1970, Hammermerster 1974, Eichhorn 1982, Brutsaert 1985).

Several catheterisation studies have shown that the careful measurement of left ventricular volumes during diastole permits one to calculate the rate of diastolic filling. Patients with disorders of left ventricular compliance have a lower diastolic filling rate than normal.

The non-invasive evaluation of left ventricular diastolic performance by gated equilibrium radionuclide angiography (ERNA) has been suggested as a reliable method of uncovering diastolic dysfunction in patients with coronary artery disease and systemic hypertension independent of left ventricular systolic function (Bonow 1981, Reduto 1981, Mancini 1983, Inouye 1984). Few reports deal with the relaxation process in volume overload hypertrophy (Haurath 1980, Osbakken 1984, Lavine 1985).

V.1.0. LEFT VENTRICULAR RELAXATION

Left ventricular relaxation is a complex, energy dependent process (Langer 1968, Katz 1973) with the sarcoplasmic reticulum playing a central role by its ability to sequestrate calcium ions. The

lowering of the calcium concentration in the vicinity of the myofibrillar proteins is thought to result in actin-myosin dissociation by inhibition of myofibrillar ATPase activity (Langer 1974).

V.2.0 PASSIVE ELASTIC PROPERTIES

The passive elastic properties of the left ventricular chamber are expressed as the ratio of the change in pressure to the change in volume. This ratio reflects left ventricular chamber stiffness, and its reciprocal, the left ventricular chamber compliance. The relationship is curvi-linear such that the left ventricle is relatively compliant at low volume but becomes progressively less so with increased volume. Therefore a comparison of stiffness in different ventricles can only be meaningful if pressure and volume are specified. Additionally, relative changes in pressure and volume are influenced by extrinsic factors, which include atrial systole, heart rate, the pericardium, arterial pressure and ventricular interaction (Grossman 1976, Ross 1979, Grossman 1980, Janicki 1980). This is in contradistinction to myocardial stiffness or compliance which is a function of the stress and strain within the wall of the ventricle (Mirsky 1973, Gibson 1974).

Chronic alterations in preload as occur in aortic regurgitation have been reported to result in major changes in left ventricular chamber stiffness (Dodge 1962, Gault 1970, Gaasch 1972, Grossman 1974). In a study by Grossman (1974), left ventricular diastolic chamber stiffness correlated well with wall thickness in a diverse group of cardiac disorders, emphasising the importance of wall thickness as a determinant of ventricular stiffness. However, in chronic volume overload, diastolic pressure has been reported to

frequently be normal despite an increase in diastolic volume (Dodge 1962); although it might be interpreted as indicating decreased ventricular stiffness (increased compliance), the slope of the pressure volume curve is usually normal or increased, suggesting normal or increased stiffness. The clinical significance of this alteration in ventricular stiffness is uncertain - it possibly limits dilatation and encourages anterograde flow of blood in the aorta during diastole by offering increased resistance to regurgitant flow.

V.3.0 VISCOUS AND INERTIAL PROPERTIES

The viscous and inertial properties of the left ventricle are of theoretical significance in the clinical setting and will not be discussed any further.

V.4.0 EFFECTS OF EXERCISE AND POSTURE

During exercise end-diastolic volume increases in most persons and end-systolic volume decreases, with a resultant increase in stroke volume and an increase in ejection fraction (Poliner 1980). With increased heart rate, the duration of diastole shortens and the proportion of the cardiac cycle available for filling is decreased, with most of the cycle devoted to systolic ejection. It follows that filling becomes more rapid to accommodate the increase in end-diastolic volume. Body position also alters ventricular volume (Poliner 1980, Reduto 1981), with the heart doing more volumetric work at a lower heart rate in the supine position, while in the upright posture at comparible workloads, delivery of cardiac output is more rate related.

V.5.0 EARLY DIASTOLIC FILLING

Early diastolic filling, in contrast to late filling caused by atrial systole, is responsible for significant filling of the ventricle before diastolic pressure reaches a minimum (Fioretti 1980). Although there are few ventricular models capable of describing the complex dynamics and interactions between pressure and volume during this part of the cardiac cycle, it is reasonable to conclude that early ventricular filling is dependent on the pressure gradient across the mitral valve and the resistance of the ventricular wall to distention.

V.6.0 SYSTOLIC-DIASTOLIC INTER-RELATIONSHIPS.

The importance of diastolic relaxation and filling to adequate systolic function has not always been well appreciated. To these "mechanical" or "primary" factors, more subtle influences can be added namely the impact of neurohumoral factors (Sonnenblick 1963, Fouad 1983), which appear to improve left ventricular contraction and enhance relaxation rate and filling (Fouad 1984). It has been shown that the velocity of lengthening is directly related to the extent of preceding shortening, and when using equilibrium radionuclide angiocardiography this means the relationship between peak filling rate or the velocity of lengthening and ejection fraction or the extent of shortening (Bonow 1981, Polak 1982, Bahler 1983). Consequently, for proper comparisons between patient groups and during interventions within a group, the peak velocity of filling must be related to the concurrent extent of systolic shortening.

V.7.0 NON-INVASIVE RADIONUCLIDE VARIABLES OF DIASTOLIC FUNCTION

Radionuclide derived peak filling rate (PFR), expressed as end-

diastolic volumes per second, correlates best with haemodynamic variables that reflect active rather than passive diastolic function (Gaasch 1976, Rankin 1980). It is defined as the late positive peak of the first derivative of the volume curve. It correlates with left ventricular end-diastolic pressure which depends on both cardiac and non-cardiac factors (Braunwald 1963). In addition, it shows a strong correlation with the systolic haemodynamic variable ejection fraction, demonstrating the integral coupling of cardiac contractility to myocardial relaxation. Average diastolic filling rate (ADFR), which averages filling from end-systole to the end of the R-R interval, has more recently been used in accessing rapid ventricular filling in both physiologic and pathologic hypertrophy (Smith 1985).

In a recent gated blood scintigraphic study (Lavine 1985), the abnormal pattern of resting diastolic filling of the left ventricle in patients with moderate to severe chronic symptomatic and asymptomatic aortic regurgitation is reported. Peak filling rate (PFR) was lower in the aortic regurgitation group than in normal subjects (2.24 ± 0.70 versus 3.09 ± 0.71 EDV/Sec, $p < 0.001$). Similarly, average diastolic filling rate (ADFR) was lower in the aortic regurgitation group (1.31 ± 0.40 versus 1.63 ± 0.29 EDV/Sec, $p < 0.01$). They also showed that diastolic filling patterns were not significantly different in asymptomatic and symptomatic groups and did not differentiate patients with congestive heart failure or more severe aortic regurgitation from those with less severe disease.

Time to peak filling rate (TPFR) is the time from end-systole (derived from the volume curve) to the occurrence of peak filling

(derived from the first derivative of the volume curve). Although not reported to be independently useful, in combination with a reduced peak filling rate it increases the sensitivity for the detection of coronary artery disease (Bonow 1981, Kemper 1981). When calculated during exercise, it must be normalised for the heart rate(R-R interval).

V.8.0 LIMITATIONS

Despite the recent interest in the use of equilibrium radionuclide angiocardiography to assess diastolic function in a varied number of cardiac conditions, there are important limitations in the technique:

(i) The timing of events during the cardiac cycle is not accurate because mitral valve opening and mitral valve closure are not accurately delineated and thus time to peak filling rate contains both isovolumic relaxation as well as early diastolic filling. As a result, interpretation of the anomalies in this interval are difficult (Grossman 1980).

(ii) Fundamental differences exist in the rest and exercise measurement of peak filling rate - at rest the contribution of atrial systole can easily be identified and excluded, but at peak exercise with a much shorter R-R interval, atrial systole may be a major determinant of the measured peak filling rate.

(iii) The forward-backward reformat technique more accurately characterises the correlation of filling rates and later diastolic curve events, but this elegant technique requires considerable computer memory space and is thus not applicable to exercise studies where evaluation needs to be made at numerous levels of exercise.

CHAPTER VI

METHODOLOGY

VI.0.0 INTRODUCTION

This study was a prospective, sequential evaluation of left ventricular function using both non-invasive and invasive techniques in symptomatic and asymptomatic patients with isolated chronic, severe (4+) AR at cardiac catheterisation.

The aims of the study were to:

(I) Identify differences in the clinical, echocardiographic, resting and exercise haemodynamic and radionuclide measures of left ventricular function in symptomatic and asymptomatic patients with chronic severe AR with particular reference to the incidence of presymptomatic development of left ventricular dysfunction.

(II) Critically evaluate the role of exercise stress (both isotonic and isometric) in the assessment of patients with chronic severe AR.

(III) Evaluate the influence of time (sequential studies) on the haemodynamic burden in asymptomatic patients.

(IV) Study the impact of successful aortic valve replacement on the reversibility of abnormal pre-operative LV function in an attempt to predict which patients would benefit from this therapeutic intervention and whether operation for symptoms alone is the correct clinical practice.

VI.1.0 STUDY DESIGN:

This was a prospective analysis of 60 patients with chronic severe aortic regurgitation seen at the Cardiac Clinic, Groote Schuur

Hospital, Cape. Patients of both sexes between the ages of 13 and 65 years were included. Thirty two(32) symptomatic patients were identified following consultation in the Cardiac Clinic and referred for cardiac catheterisation prior to aortic valve replacement. Twenty eight(28) asymptomatic patients with severe aortic regurgitation who were being seen regularly in our Outpatients Department were also evaluated.

The details of the study design are summarised in Figure 6.1. It should be noted that only 22 symptomatic patients underwent aortic valve replacement, the other 10 patients declining surgery. Three patients died postoperatively at 17 days, 2 months and 6 months respectively, resulting in the re-evaluation of 19 patients at 6 months following valve replacement surgery. Twenty three (23) asymptomatic patients and three of the symptomatic group who declined operation (total n = 26) underwent sequential assessment at 6 months following the initial evaluation. Only 9 patients (8 asymptomatic and 1 symptomatic) agreed to follow up study at 12 months. The design and performance of this study was approved by the Ethics and Research Committee of the University of Cape Town Medical School on the 13th April 1983. Informed consent was obtained by the author according to the Declaration of Helsinki. All aspects of the assessment, namely clinical evaluation, rest and exercise equilibrium radionuclide angiocardiography and cardiac catheterisation were performed personally by the author. Echocardiography was performed by experienced echocardiographers.

VI.1.1 Clinical Assessment.

All patients were evaluated on admission to hospital. A detailed history was obtained with particular reference to:-

(i) Dyspnoea on effort classified according to the New York Heart Association criteria (1973).

(ii) The presence of typical ischaemic or atypical praecordial chest pain.

(iii) The presence or absence of palpitations.

(iv) Symptoms of orthopnoea, nocturnal dyspnoea or ankle swelling.

(v) A history of acute rheumatic fever in the past.

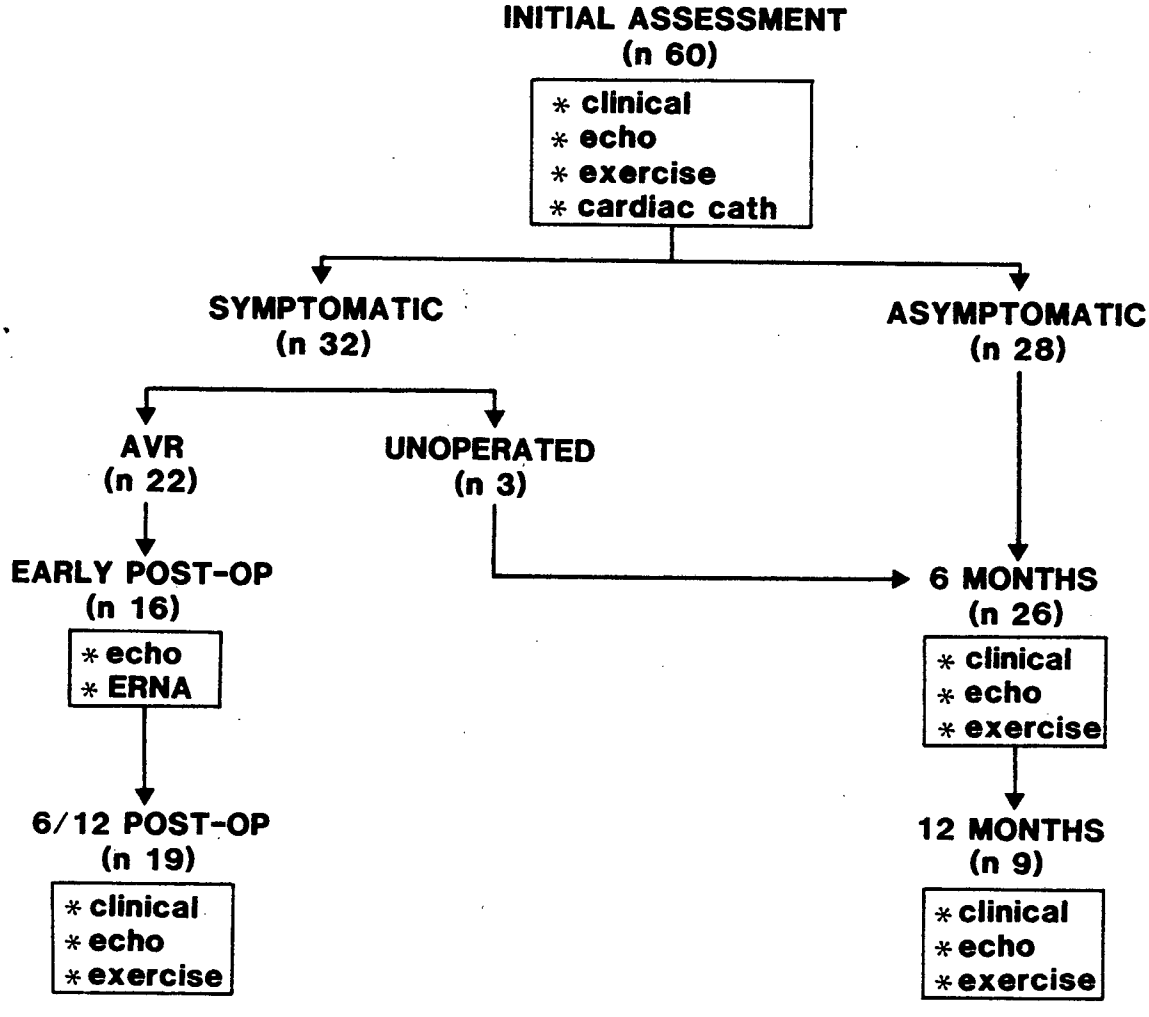
In the symptomatic patients every effort was made to accurately establish the exact time of onset of symptoms.

Physical examination included characterisation of the peripheral pulse, the presence of peripheral signs of aortic regurgitation including Corrigan's sign in the neck, pistol-shot femoral pulses and Durozíezs' sign. The blood pressure was measured with a standard sphygmomanometer, taking phase IV Korotkow sound (muffling) as the diastolic pressure. In addition, the presence or absence of signs of congestive heart failure were noted, namely an elevated jugular venous pressure, pedal and/or sacral oedema and hepatomegaly. Finally, localisation and characterisation of the cardiac apex and a number of auscultatory phenomena, namely the intensity of the 1st heart sound, the presence of a middiastolic rumble at the apex and the intensity and length of the basal early diastolic murmur were recorded.

A 12-lead electrocardiogram was recorded in every patient, and note taken of the rhythm, P-R interval and the degree of left ventricular hypertrophy as judged by the Romhilt-Estes voltage criteria (Romhilt-Estes 1968) - the largest R or S wave in the limb leads equal to or greater than 20mm, the largest S wave in V1 or V2

equal to or greater than 30mm, the largest R wave in V5 or V6 equal to or greater than 30mm. The Sokolow-Lyon index (Sokolow-Lyon 1949) namely the sum of the S wave in V1 plus the larger of the R wave in V5 or V6 greater than or equal to 45mm in the absence of ST-T wave abnormalities or greater than or equal to 35mm in the presence of ST-T wave changes was also used.

Figure 6.1 STUDY DESIGN



A standard chest radiograph (posterior-anterior and lateral at 6ft) also formed part of the evaluation. The cardiothoracic ratio was calculated from the frontal posterior-anterior film by dividing the maximal frontal width of the heart, excluding the apical fat pad, by the internal width of the chest at the level of the dome of the

right hemidiaphragm (Chikof 1977). The lung fields were assessed as being normal, or demonstrating upper lobe blood diversion or interstitial pulmonary oedema.

This clinical assessment was repeated at six monthly intervals in the asymptomatic patients and at six months postoperatively in the symptomatic patients who underwent successful aortic valve replacement.

VI.1.2 Echocardiography.

Echocardiography was performed on all patients during their hospital admission. This was repeated at six monthly intervals in the asymptomatic group and performed at 10 days and six months postoperatively in those symptomatic patients who underwent successful aortic valve replacement.

M-mode echocardiograms were obtained using an Aloka SSD-800 phased array ultrasonoscope equipped with a 2.3-megaHertz focused transducer interfaced with a Honeywell LS6B high resolution CRS Visicorder. All recordings were made at 100mm/sec paper speed with a simultaneously recorded electrocardiogram. Patients were examined in the supine position with slight cranial tilt with the transducer applied along the left sternal border at that interspace from which the mitral echogram could be visualised with the transducer held perpendicular to the chest wall with only slight medial and no superior or inferior angulation. From this position the transducer was gradually tilted inferolaterally until the echoes of the mitral valve were replaced by those of the chordae tendineae with clear visualisation of the endocardium of the left side of the interventricular septum and of the posterior wall (Popp 1975).

Left ventricular dimensions at end-diastole (DED) were measured at the R wave of the electrocardiogram and the end-systolic dimension (DES) was measured as the smallest vertical dimension between the left septal echo and the posterior wall endocardium. In addition, these dimensions were normalised for body surface area.

Posterior wall thickness (Th) was measured at end-diastole from the leading edge of the epicardial echo to the leading edge of the endocardial echo, with the gain adjustment set to minimise the width of these signals. A similar technique was used to measure septal thickness.

The fractional shortening (FS), expressed as the percentage change in left ventricular dimension from end-diastole to end-systole was calculated as:-

$$FS = (DED - DES/DED) \times 100$$

(MacDonald 1972, Fortuin 1972).

Because of the limitations involved in estimating left ventricular volume measurements by echocardiography (Linhart 1975), the dimension at end-diastole was used as an index of end-diastolic volume.

The cross sectional area (CSA) of the ventricular wall in a transverse plane was used as an index of myocardial mass. This method, first developed by Sasayama et al (1976), has been used in the serial follow up of changes in left ventricular mass in both clinical and experimental studies (Gaasch 1978, Schuler 1979).

It is a useful index since it incorporates directly two measurable determinants of mass, i.e. wall thickness and the minor diameter of the left ventricle. However, it is assumed that the mean wall

thickness of the whole ventricle can be approximated by the posterior wall thickness (PWTh) in the absence of asymmetric septal hypertrophy or coronary heart disease.

$$CSA = \pi \frac{(EDD}{2} + PWTh)^2 - \pi \frac{(EDD)}{2}^2$$

The relative wall thickness of the left ventricle (radius to thickness ratio) as a measure of appropriate left ventricular hypertrophy was determined as:-

$$R/Th = DED/2.Th$$

This index is linearly related to the end-diastolic volume to mass ratio within a broad range of dimensions and mass. The product of systolic blood pressure, as measured by the cuff technique, and the end-diastolic radius to thickness ratio was used as an index of peak systolic wall stress (Grossman 1975, Gaasch 1979). The rationale for the use of end-diastolic geometry is based on the observation that LV dimension and thickness at the time of peak systolic stress (in the normal ventricle) is almost equal to LV dimension and wall thickness at end-diastole (Grossman 1975).

VI.1.3 Rest and Exercise Equilibrium Radionuclide Angiocardiography.

Supine and semi-erect (45^{o}) bicycle exercise and isometric handgrip exercise was performed in all patients. After obtaining informed consent, patients were transferred to the Cardiac Catheterisation Laboratory. All patients were studied in the non-sedated, postabsorptive state (Brown 1983).

Under local anaesthesia with 5ml of a 1% Lignocaine solution, a balloon tipped triple-lumen Swan-Ganz catheter (93A-131-7F,

American Edwards Laboratory, Santa Anna CA) was introduced into the right subclavian vein using a modified Seldinger technique and the supraclavicular approach. It was advanced to the right atrium, right ventricle and main pulmonary artery to one of the branches of the right pulmonary artery supplying the right lower lobe under direct fluoroscopic screening. The position of the catheter was considered acceptable when satisfactory pulmonary capillary wedge pressure measurements were obtained after balloon inflation. Patients were then transferred to our exercise laboratory for further evaluation.

Each patient was familiarised with the exercise apparatus prior to the commencement of the exercise study. This evaluation was repeated at six monthly intervals in the asymptomatic group and six months postoperatively in the patients who underwent successful aortic valve replacement.

Exercise was performed on an Engineering Dynamic Corporation Model No. 8430 Hi-Low Cardiac Stress Testing System consisting of an imaging table with an integral multiple position bicycle ergometer and a mobile ergometer control unit.

Pulmonary artery and pulmonary capillary wedge pressures were measured using an Altech Physiological Transducer Model No. MS10-E and an Elema Schonander Mingograf EM1600.161 Multipurpose Polygraf Biomedical Recording System.

A Siemens L.E.M. Scintillation Camera with a high resolution collimator interfaced to an A^2 Medical Data System dedicated minicomputer was used to acquire radionuclide data.

Arterial pressure was recorded with a standard Baumanometer Model

300 Sphygmomanometer and cardiac output was measured with an Edwards Laboratories 9520A Cardiac Output Computer. Handgrip isometric exercise was performed using a Meredith Registered Design 861405 Handgrip Dynamometer.

VI.1.3.1 Exercise Protocol

Patients were first studied in the supine position with the bicycle ergometer so positioned that the legs were elevated above the chest. In addition, a three minute period of isometric handgrip exercise at 33% of maximal grip strength was performed in the supine position. Exercise consisted of compressing a callibrated dynamometer with the dominant hand. Maximal handgrip strength was determined as the greater of two consecutive brief maximal efforts, and following two minutes of rest, the patient performed three minutes of handgrip isometric exercise at 33% of his or her determined maximum. The level of tension was regularly checked and the patient instructed to make minor correction as indicated. In addition, patients were encouraged to breathe normally.

Graded, three minute levels of exercise were commenced at an external workload of 150 kilopond-metres (k.p.m.) per minute and increased by 150k.p.m. per level in males and by a 100k.p.m. per level in females until limited by shortness of breath or leg fatigue or both. Pedal speed was held constant at 50 to 60 revolutions per minute. Data were acquired during the last two minutes of each three minute period.

A rest period of 15 minutes was interspaced between supine and semi-erect bicycle exercise, which was then performed with a 45^{o} cranial tilt of the imaging table. The 45^{o} semi-sitting position was used as it provides maximum patient comfort during bicycle

exercise without the excessive leg fatigue commonly experienced in the supine position. In addition, it enables near-optimal camera head positioning and also simulates upright physiologic conditions. Over a two minute period patients were gradedly taken up to their maximal supine external workload. The order of exercise was not randomised. Patients were verbally encouraged to exercise until peak tolerance and instructed to gently hold but not grip the hand supports to avoid isometric contraction.

VI.1.3.2 Haemodynamic Data Acquisition

Baseline heart rate, blood pressure, cardiac output, pulmonary artery and pulmonary capillary wedge pressures were recorded.

Heart rate was obtained from the simultaneously recorded electrocardiogram during pressure measurements.

Arterial pressure was recorded in duplicate by the cuff technique using a standard Baumonometer Model 300 Sphygmomanometer and taking the phase 4 Korotkow sound (muffling) as the diastolic pressure. Mean arterial pressure was calculated as the diastolic pressure plus one third of the pulse pressure.

The thermodilution technique (Ganz 1971, Forrester 1972) was used to measure cardiac output at rest and during each level of bicycle exercise. Multiple syringes were prefilled with exactly 5ml of a sterile 5% solution of dextrose in water, and then capped so that sterility was maintained. The syringes were then placed in an ice bath at $0^{o}C$ and allowed to equilibrate for a minimum of 20 minutes. The syringe's barrel was submerged in the bath so that its contents were below the bath's level. Additionally, a syringe filled with a 5% solution of dextrose in water was placed in the icebath with the

plunger removed in order to accommodate a temperature sensing probe from the Edwards Laboratories 9520A Cardiac Output Computer. The sensing probe was placed inside the barrel so that at least two thirds of its length was submerged in the indicator. When ready for use, the syringes with injectate were removed from the bath, care being taken to ensure minimal handling of the barrel, connected to the catheter, and injected without hesitation. A minimum of three determinations were made at each level of exercise and the mean value taken. Cardiac index was derived by dividing the cardiac output by the body surface area.

Phasic and mean pulmonary artery and pulmonary capillary wedge pressures were measured from a zero level in the fourth right intercostal space in the mid-axillary line over at least two respiratory cycles. Recordings were made on an Elema-Shonander Mingograph EM1600.161 Multipurpose Polygraf Biomedical Recording System at a paper speed of 25mm/sec. These recordings were made at rest, during isometric and at each level of supine and semi-erect exercise.

Stroke volume index, stroke work index and systemic vascular resistance were derived from the above values using the following formulae:-

Stroke Volume Index = Cardiac Index in ml/min. divided by heart rate and expressed as ml/b/M^2.

Stroke Work Index = Cardiac Index in L/min. multiplied by 13.6 multiplied by the difference between the mean arterial pressure and the pulmonary capillary wedge pressure divided by the heart rate.

Pulmonary capillary wedge pressure was considered to be equivalent to left ventricular end-diastolic pressure. (Mitral valve disease was excluded at echocardiography and cardiac catheterisation in all patients).

Systemic Vascular Resistance = mean arterial pressure in mmHg divided by the cardiac output in L/min.

The following are the predicted maximum heart rates in the various age categories (from the proceedings of the National Workshop on Exercise in 1969):-

Age by Decade	Maximal Heart Rate
20 - 29	190
30 - 39	182
40 - 49	179
50 - 59	171
60 - 69	164

VI.1.3.3 Radionuclide Data Acquisition

Equilibrium radionuclide angiocardiography(ERNA) was performed after in vitro labelling of red blood cells with 30 millicuries (1110 megabequerels) of Technetium-99m Sodium Pertechnetate using the Brookhaven National Laboratory (BNL) Red Blood Cell technique (see Appendix I for details). Electrocardiographic gating was performed using the praecordial lead giving the largest R-wave deflection.

Rest and Exercise Equilibrium Radionuclide Angiocardiographs were performed using a Siemens Low Energy Mobile (L.E.M) Scintillation Camera with a high resolution collimator interfaced to an A^2 Medical Data System dedicated single terminal minicomputer.

Data acquisition was performed at rest and during the last two minutes of each three minute bicycle exercise level in 64 x 64 byte mode at 24 frames per R-R interval. Images were acquired in an approximately 45° Left Anterior Oblique (LAO) view which provided best septal separation. This provided ± 200,000 counts per frame. Patient data was stored on removable 2.5mB discs for subsequent analysis.

Visually interpretable information is produced within 30 seconds of the onset of data acquisition, and statistically reliable results are available within one to two minutes (Bacharach 1977, Borer 1978). Because blood radioactivity is proportional to blood volume, quantitation of radioactive emissions collected from the left ventricle after background correction, permits direct determination of relative left ventricle volume; the collection of such information over many successive intervals permits determination of average ejection fraction (EF) with a high degree of precision (Green 1978).

VI.1.3.4 Radionuclide Data Analysis

The left anterior oblique images at rest and at each exercise level were analysed to determine ejection fraction and average and peak diastolic filling rate. Visual analysis was performed by two experienced observers viewing the studies in endless-loop cine display format using the M.D.S.A$_2$ Multiterminal System and commercially available software (A$_2$ MUGE Programme with automatic edge detection and background correction).

All image data was temporarily and spatially filtered using 9 point filters. To generate a volume curve, the edges (regions of interest) of the left ventricle for each image in the study were

detected using the filtered data and the M.D.S. MUGE Programme which detects the edges by means of second derivative and threshold values.

A background region is automatically generated by the computer inferolateral to the systolic image of the left ventricle. This region is verified by the operator, or a manually drawn region may be substituted if the computer-generated background region impinges excessively on the screen.

Subsequently, a background corrected time-activity curve is generated from the computer defined region of interest and this is used for the calculation of the left ventricular ejection fraction. This is calculated as background corrected end-diastolic counts minus end-systolic counts divided by end-diastolic counts. Peak and average emptying and filling rates are calculated from the first derivative of this time-activity curve.

A histogram of the number of beats versus the beat length (the R-R histogram) is automatically generated during acquisition and this was viewed to determine the stability of the electrocardiogram.

This sequence was repeated for each level of study and as previously noted, this exercise protocol was repeated at six monthly intervals in the asymptomatic group and six months postoperatively in those patients who underwent successful aortic valve replacement.

The normal values and the correlation co-efficients (R) representing the validation, reproducibility and inter- and intra-observer variability of the rest radionuclide ejection fraction in our laboratory are in Appendix II.

VI.1.4 Cardiac Catheterisation.

Cardiac catheterisation was performed within 24 to 48 hours of the exercise evaluation in all patients. The purpose of the procedure was to confirm the severity of aortic regurgitation and exclude other valvular and coronary artery disease. All patients were studied in the post absorptive state, using Clonazepam 1mg, one hour prior to the procedure, for sedation.

Under local anaesthesia with 10ml of a 2% Lignocaine solution, via a modified Seldinger approach to the right groin, a number 7 Cournand Catheter (Size 7 French 125cm USCI Cournand Cardiovascular Catheter No. 007456) was introduced to the right femoral vein and advanced via the right atrium, right ventricle, and pulmonary artery to the wedge position. Critically damped pressure recordings were obtained through this fluid-filled catheter using a Statham P23Id Pressure Transducer and recorded on an Electronics for Medicine VR12 Recorder System.

A No. 8 Pigtail Catheter (Size 8 French 110cm USCI/Positrol II tight radius Pigtailed Cardiovascular Catheter No. 007818) was introduced to the right femoral artery and passed retrogradely up the aorta and through the aortic valve into the left ventricle. Critically damped pressures were recorded using an identical recording system.

Cardiac output was measured by the indicator dye technique of Hamilton et al (1948) using 5mg of Indocyanine Green. Forward stroke volume was derived by dividing the cardiac output by the heart rate at the time of measurement.

Left ventriculography was performed in a single-plane 30° right

anterior oblique projection with the pigtail catheter positioned 2-3cm above the aortic valve to avoid ventricular irritability. Sixty millilitres(60) of Jopamiron 300 (Iopamidol) was injected over three seconds using an Angiomat 3000 (Sybron Medical Products Division) Power Injector. The left ventricular angiograms were exposed on 35mm film at 60 frames per second using a Phillips nine inch image intensifier system. Subsequently left ventricular volumes were calculated using the area length method of Dodge et al (Dodge 1968) after adjustment for radiologic enlargement and distortion, the coefficient being determined by means of a grid positioned at the mid-thoracic level. Left ventricular volumes were quantitated from a well opacified sinus beat, not preceeded by an extrasystole. Angiographic stroke volume was calculated as the difference between the end-diastolic and end-systolic volumes and the left ventricular ejection fraction derived as the ratio of stroke volume to end-diastolic volume. Angiographic cardiac index was derived by multiplying angiographic stroke volume index by heart rate at the time of the study.

Cine aortography was performed after left ventriculography in a 60° left anterior oblique projection. Catheter placement was as described above and 60ml Jopamiron 300 was injected over 3 seconds and the studies recorded on 35mm cine film at 60 frames per second. The angiographic severity of the aortic regurgitation was agreed upon by two independent observers according to the following grading system (Grossman 1980):-

1+ = faint opacification of part of (but not the entire) left ventricle, which clears with each systole;

2+ = left ventricular opacification to a degree less than that in the aorta, but which does not clear with each beat;

3+ = left ventricular opacification equal to that of the aorta;

4+ = complete and dense left ventricular opacification in one beat with an eventual density of contrast greater than that in the aorta.

Selective left and right coronary angiography was subsequently performed in all patients using 8/4 left and right Judkins Catheters (Size 8 French 100cm USCI/Positrol II Judkins Type 4cm Left or Right Coronary Taper Tipped Cardiovascular Catheters). The coronary angiograms were routinely obtained in various angles of right and left anterior oblique projection. Eight to ten millilitres of Jopamiron 370 were injected over 2-3 seconds and the studies recorded on 35mm cine film at 50 frames per second.

Quantitative evaluation of cine aortography in the assessment of aortic regurgitation was then performed in a group of these patients using a Size 7 French Carolina Medical Electronics Square Wave Electromagnetic Flowmeter (Model FM501). Zero flow reference was determined extravascularly by inserting the catheter into 50ml of the patients blood withdrawn prior to this part of the study. The electromagnetic flowmeter probe was then inserted and retrogradely passed up a Size 8 French 59cm USCI Mullins Transseptal Catheter Introducer Sheaths (No. 008552) and positioned 2-3cm above the aortic valve. In this way the probe was centred in the lumen of the ascending aorta. The area beneath the flow curve, above and below zero reference, were planimetered and the percentage regurgitation was calculated from the formula:-
Percentage regurgitation = area of negative flow divided by area of forward flow.

This part of the study was designed to assess the accuracy of

qualitative angiographic grading, by comparing it to the quantitative angiographic technique (Sandler 1963, Hunt 1973) and the above electromagnetic flowmeter technique (Mennel 1972).

VI.2.0 DATA ANALYSIS:

Patients were divided into symptomatic and asymptomatic groups. Further division was based on the LV ejection fraction response to exercise.

Analysis of variance (Winer 1971) was performed to analyse serial changes in echocardiographic, haemodynamic and radionuclide data. Paired t test was used to compare pre-operative and postoperative measurements and the unpaired t test was used to compare different patient groups. A p value <0.05 was considered significant.

All data are expressed as mean values $\pm$ 1 standard deviation.

CHAPTER VII

RESULTS

VII.0.0 INTRODUCTION

Sixty (60) patients were entered into this prospective evaluation of left ventricular function in severe aortic regurgitation. Thirty two (32) of these patients were symptomatic and admitted to the Cardiac Clinic beds for assessment prior to aortic valve replacement - these patients constitute Group 1. Twenty eight (28) asymptomatic patients with clinically severe chronic aortic regurgitation were admitted for comparison and sequential assessment and constitute Group 2.

VII.1.0 CLINICAL CHARACTERISTICS

At the time of first assessment the clinical characteristics of the two groups of patients were:-

VII.1.1 Age

Symptomatic group : 14 to 66 years (mean 32 years)

Asymptomatic group : 16 to 44 years (mean 24 years).

VII.1.2 Sex

	Males	Females
Symptomatic group :	17	15
Asymptomatic group :	24	4

VII.1.3 Aetiology

In the symptomatic group -

- 14 patients (44%) gave a history consistent with a previous episode of acute rheumatic fever.
- 4 patients (12.5%) had a documented episode of infective

endocarditis in the past.

- 2 patients (both older; 63 years and 66 years) were considered to have syphilitic aortic valve disease on the basis of positive serology.
- in twelve patients (38%) the aetiology is unknown.

In the asymptomatic group -

-14 patients (50%) gave a history of a previous episode of acute rheumatic fever.

-two patients (ages 38 and 44 years) had serology positive for syphilis.

- one patient had a bicuspid aortic valve.
- in eleven patients (39%) the aetiology is unknown.

VII.1.4 Symptoms

VII.1.4.1 SOB:

All 32 symptomatic patients gave a history of dyspnoea on effort:-

NYHA Class	Number
I	0
IIA	8 (25%)
IIB	21 (62%)
III	3 (13%)
IV	0

Although the majority of patients had dyspnoea on moderate exercise, 10 patients had a previous episode of congestive heart failure prior to referral which had responded promptly to routine therapy for congestive heart failure(CHF). At the time of evaluation 7 of this group were Class IIB limited, 2 were Class III limited and 1 patient was only short of breath on extreme effort.

VII.1.4.2 Duration:

The duration of symptoms ranged from 1 to 130 months with a mean duration of 16 ± 4 months. In the subgroup of patients who had presented with an episode of CHF, the mean duration of SOB was 14 ± 17.5 months with a range of 1 to 60 months.

VII.1.4.3 Atypical Chest Pain:

Eighteen patients in group 1 (56%) gave a history of atypical, sharp left praecordial chest pain of short duration which was self-limiting and usually occurred at night. Eight asymptomatic patients (29%) volunteered transient short-lived atypical left praecordial chest pain.

VII.1.4.4 Palpitations:

Fifteen patients (47%) in the symptomatic group had experienced occasional, short-lived, rapid, regular palpitations which were almost exclusively effort related and not associated with any other symptoms.

VII.1.4.5 Medication

At the time of initial evaluation nineteen patients (59%) in the symptomatic group were receiving treatment for heart failure. Medication included digoxin and diuretics (furosemide or amiloride 5mg + hydrochlorothiazide 50mg). Medication was discontinued at least 48 hours prior to exercise and invasive evaluation.

VII.1.5 Physical Findings:

All patients, both symptomatic and asymptomatic, had the clinical features of severe aortic regurgitation, namely a wide pulse pressure, a positive Du Roziez's sign, a soft or inaudible first

heart sound and a basal early diastolic murmur. In addition, most patients had an Austin-Flint mid-diastolic rumble at the apex. The mean pulse pressure was similar in the two groups (Group 1 115 ± 34mmHg; Group 2 121 ± 23mmHg).

VII.1.6 Electrocardiogram

All patients were in sinus rhythm. The PR interval ranged from 0.16 - 0.40 sec (mean 0.20 ± 0.05sec). All but two symptomatic patients had left ventricular hypertrophy with repolarisation change as assessed by the Sokolow-Lyon index. Similarly, all but two asymptomatic patients had left ventricular hypertrophy with repolarisation change.

VII.1.7 Chest Radiograph

Every patient had a standard postero-anterior and lateral chest radiograph. The cardio-thoracic ratio was similar, 0.47 to 0.69 (mean 0.59 ± 0.05) in the symptomatic group and 0.44 to 0.69 (mean 0.55 ± 0.06) in the asymptomatic patients. The lung fields were assessed as being normal in all patients at the time of initial evaluation.

Table 7.1 overleaf summarises the clinical details in the two groups of patients.

The subsequent stepwise evaluation of these two groups of patients is summarised in Figure 6.1(see page 104) and will be discussed as follows:-

1. INITIAL ASSESSMENT.
2. POSTOPERATIVE EVALUATION.
3. SEQUENTIAL STUDIES.

Table 7.1: CLINICAL PROFILE

	Symptomatic n = 32	Asymptomatic n = 28
Age (years)	32 (14 - 66)	24 (16 - 44)
Sex - Male	17	24
Female	15	4
Aetiology:		
RH. Fever	14	14
Inf. Endocarditis	4	0
Syphilis(positive serology)	2	2
Bicuspid AV	0	1
Unknown	12	11
NYHA Class:		
I	0	28
IIA	8	
IIB	21	
III	3	
IV	0	
Duration (Months)	16 ± 4 (1-130)	
Atypical Chest Pain	18	8
Palpitations	15	0
Pulse Pressure (mmHg)	115 ± 34	121 ± 23
CTR	0.59 ± 0.05	0.55 ± 0.06

VII.2.0 INITIAL ASSESSMENT

The initial non-invasive and invasive evaluation of the two groups of patients included:-

(a) M-mode echocardiography.

(b) Isometric and isotonic symptom-limited bicycle exercise in

both the supine and semi-erect positions.

(c) Cardiac catheterisation.

VII.2.1 M-MODE ECHOCARDIOGRAPHY:

The echocardiographic measurements of LV dimensions and wall thickness and the derived measures of LV volume, mass, systolic function and systolic wall stress in the two groups of patients are summarised in tables 7.2 and 7.3. Technically satisfactory recording enabling accurate measurements were available in 28 of the 32 symptomatic patients and in all (28) of the asymptomatic group.

Appendix III tabulates the range of echocardiographic measurements in patients with compensated, borderline and decompensated chronic aortic regurgitation as compared to normal values(Gaasch 1983).

VII.2.1.1 SYMPTOMATIC GROUP (n = 28):

LV Dimensions:

The LV DED in this group of patients ranged from 5.0 to 9.7cm with a mean of 6.9 $\pm$ 1.1cm. All but two patients had echocardiographic evidence of LV enlargement and 5 patients (18%) had marked LV dilatation (LV DED > 8.0cm). Indexing these measures for body surface area, 17 patients (61%) fell into the decompensated range of >4.0cm/m^2. The LV DES ranged from 2.6 - 7.7cm (mean 4.7 $\pm$ 1.1) and 7 patients (28%) had a LV DES > 5.5cm. Similarly, when corrected for body surface area, 17 patients (61%) were in the decompensated range of >2.6cm/m^2.

Table 7.2: ECHOCARDIOGRAPHIC MEASURES IN THE SYMPTOMATIC PATIENTS (n = 28):

PT.	DED	DEDI	DES	DESI	FS	PWT	R/Th	SWS	CSA	ESV	PSP	PSP/ESV
M.A.	7.2	3.8	4.8	2.5	33	1.1	2.5	589	29	67	180	3.8
F.A.	7.6	5.1	4.9	3.3	35	1.5	2.5	456	43	70	180	2.6
R.A.	7.6	4.5	5.5	3.3	28	1.0	3.8	608	27	88	160	1.8
M.B.	9.7	4.9	7.7	3.9	21	1.1	4.4	1004	37	173	230	1.3
B.B.	8.3	5.3	5.0	3.2	40	1.2	3.5	588	36	73	170	3.8
R.C.	8.4	4.2	5.5	2.8	34	1.0	4.2	651	30	88	155	1.8
D.D.	5.3	4.0	3.4	2.6	36	1.2	2.2	331	25	34	150	4.5
MdV	7.0	4.7	4.4	3.0	37	1.6	2.2	306	43	57	140	2.5
E.G.	7.7	5.1	5.0	3.3	35	1.1	3.5	560	30	73	160	2.2
K.G.	6.0	3.1	4.0	2.0	33	1.6	1.9	300	38	47	160	3.4
M.H.	8.6	4.0	6.0	2.8	30	1.5	2.9	401	48	105	140	1.3
B.H.	6.7	3.9	5.0	2.9	25	1.2	3.2	475	33	73	150	2.1
E.J.	6.5	3.9	4.3	2.6	34	1.2	2.7	542	29	54	200	3.7
J.L.	8.6	5.3	6.7	4.1	22	1.3	3.3	430	41	131	130	1.0
N.L.	7.4	4.7	5.6	3.5	24	1.0	3.7	592	26	92	160	1.8
R.L.	5.0	2.7	2.6	1.4	48	1.3	2.9	269	26	20	140	7.1
M.L.	6.8	4.0	5.8	3.4	15	0.8	4.3	595	19	98	140	1.4
S.M.	6.2	4.1	3.7	2.4	40	1.0	3.1	465	23	40	150	3.8
H.M.	6.0	3.8	3.7	2.3	38	1.3	2.3	439	30	40	190	4.8
H.M.	7.2	4.6	5.2	3.3	28	1.2	3.0	450	32	79	150	1.9
M.N.	7.1	4.3	4.6	2.8	35	1.3	2.8	443	35	62	160	2.6
E.N.	6.0	3.9	4.1	2.7	32	1.1	2.7	382	26	49	140	2.4
J.N.	6.2	4.3	4.2	2.9	32	0.9	3.4	482	20	52	140	2.7
N.P.	6.6	4.4	4.7	3.1	29	1.5	2.2	330	38	64	150	2.3
P.P.	5.7	3.4	3.2	1.9	44	0.8	3.6	499	16	30	140	4.7
M.vB	6.2	3.2	4.6	2.4	25	1.0	3.1	465	23	62	150	2.4
E.vH	6.7	4.0	4.4	2.7	34	1.0	3.9	663	28	57	170	4.8
M.vW	5.9	3.8	3.5	2.3	41	1.2	2.5	435	27	46	175	3.8
MEAN	6.9	4.2	4.7	2.8	32	1.2	3.0	489	31	68	160	3.0
±S.D.	1.1	0.7	1.1	0.6	7	0.2	1.7	22	8	32	22	1.4

DED = Dimension at end-diastole
DEDI = Dimension at end-diastolic indexed
DES = Dimension at end-systole
DESI = Dimension at end-systole indexed
FS = Fractional Shortening
PWT = Posterior wall thickness
R/Th = Radius-to-wall thickness ratio
SWS = Systolic wall stress
CSA = Cross-sectional area
ESV = End-systolic volume
PSP = Peak systolic pressure

Table 7.3: ECHOCARDIOGRAPHIC MEASURES IN THE ASYMPTOMATIC PATIENTS (n = 28):

PT.	DED	DEDI	DES	DESI	FS	PWT	R/Th	SWS	CSA	ESV	PSP	PSP/ESV
S.A.	6.3	4.2	4.2	2.8	33	1.0	3.2	473	23	52	150	2.9
L.A.	7.1	4.6	4.8	3.1	32	1.2	3.0	473	31	67	160	2.4
S.A.	7.6	4.5	5.2	3.1	32	0.8	4.8	950	21	82	200	2.4
M.B.	6.7	4.2	4.2	2.7	36	0.7	4.8	670	16	52	140	2.7
S.C.	5.9	3.5	3.8	2.3	36	1.0	3.0	354	22	42	120	2.9
A.C.	7.6	5.5	5.0	3.6	34	1.3	2.9	409	36	73	140	1.9
G.D.	7.2	4.3	4.8	2.9	33	1.2	3.0	480	32	67	160	2.4
D.D.	7.3	3.9	4.8	2.6	34	1.3	2.8	477	35	67	170	2.5
H.H.	7.5	4.7	5.5	3.4	27	1.3	2.9	433	36	88	150	1.7
P.J.	6.6	4.5	4.4	3.0	33	1.1	3.0	420	26	57	140	2.5
J.J.	6.6	4.2	4.8	3.0	27	1.5	2.2	396	38	67	180	2.7
K.K.	7.2	4.5	5.0	3.1	30	1.1	3.3	491	29	73	150	2.1
S.M.	5.9	3.3	3.9	2.2	34	1.2	2.5	369	27	44	150	3.4
P.M.	7.6	5.5	4.7	3.4	38	1.0	3.8	760	27	64	200	3.1
F.N.	6.3	4.3	4.7	3.2	25	1.1	2.9	401	26	25	140	2.2
N.O.	6.8	3.5	4.1	2.1	40	1.3	2.6	418	33	49	160	3.3
M.P.	6.0	4.1	4.4	3.0	26	1.3	2.3	369	30	57	160	2.8
J.P.	6.5	3.6	3.9	2.2	40	1.2	2.7	460	29	44	170	3.8
I.R.	8.5	4.8	5.7	3.2	33	1.5	2.8	482	47	95	170	1.8
S.R.	6.0	4.0	3.8	2.5	37	1.2	2.5	375	27	42	150	3.6
W.S.	5.0	3.7	3.0	2.2	40	1.1	2.3	341	21	26	150	5.7
T.S.	7.9	4.3	4.8	2.6	39	1.1	3.5	490	30	67	140	2.1
A.T.	7.2	4.7	5.0	3.3	30	1.2	3.0	420	32	73	140	1.9
v/dS	8.2	4.5	5.4	2.9	34	1.2	3.4	547	36	85	160	1.9
L.V.	7.9	4.9	5.3	3.3	34	1.2	3.3	600	35	82	180	2.2
C.V.	5.5	3.5	3.5	2.2	36	1.0	2.8	330	20	46	120	2.6
D.V.	6.1	3.3	4.1	2.2	33	1.2	2.5	305	28	49	120	2.5
A.W.	5.2	3.5	3.6	2.4	31	1.0	2.6	416	20	38	160	4.2
MEAN	6.8	4.2	4.5	2.8	34	1.2	3.0	470	29	60	154	2.7
±S.D.	0.9	0.6	0.6	0.4	4	0.2	0.6	137	7	18	21	0.8

LV Mass and the R/Th Ratio:

The LV mass as reflected by the cross sectional area ranged from 16 to 48cm^2 (mean 31 ± 8cm^2) with only 3 patients (11%) having values in the normal range (16 ± 4cm^2).

The R/Th ratio, used as an index of the volume to mass ratio, ranged from 1.9 to 4.4 (mean 3.0 ± 1.7) with only 3 patients (11%) having values > 4 reflecting increased peak systolic stress. Peak systolic stress, the product of the R/Th ratio and peak systolic pressure, ranged from 269 to 1004 (mean 489 ± 22), with 4 patients

(14%) having values > 600mmHg.

LV Systolic Performance:

The mean fractional shortening was 33% (range 15 to 48%) with the majority (68%) of patients in the compensated and only 14% in the decompensated range of < 25%. Eighteen percent(18%) of this group had values in the borderline range. The peak systolic pressure to end systolic volume ratio (PSP/ESV) ranged from 1.0 to 7.1 with a mean of 3.0 ± 1.4.

VII.2.1.2 ASYMPTOMATIC GROUP (n = 28):

LV Dimensions:

The LV DED in this group ranged from 5.0 to 8.5cm (mean 6.8 ± 0.9). Only one patient did not have echocardiographic evidence of LV dilatation. Only 2 patients (7%) had an LV DED > 8.0cm. When this dimension was normalised for body surface area, 71% (20 patients) were in the decompensated range.

The LV DES ranged from 3.0 to 5.7cm (mean 4.5 ± 0.6), with only 2 patients (7%) having a value > 5.5cm. Five patients (18%) were in the intermediate range of 5.0 to 5.4cm. The mean of this measure indexed was 2.8 ± 0.4cm/M^2, which is in the decompensated range (>2.6cm/M^2), with 18 patients (64%) having values > 2.6cm/M^2.

LV Mass and R/Th Ratio:

The cross sectional area as a measure of LV mass ranged from 16 to 47cm^2 (mean 29 ± 7cm^2) with 3 patients (11%) having normal values.

The R/Th ratio ranged from 2.2 to 4.0 (mean 3.0 ± 0.6) with 2 patients (7%) having evidence of increased peak systolic wall

stress (value > 4) and also reflected in the product of R/Th and peak systolic pressure being > 600mmHg.

LV Systolic Performance:

The mean fractional shortening was 34 ± 4% in this group with a range of 25 to 40%. No patients were decompensated as reflected by this measure. The mean PSP/ESV as a measure of contractility was 2.7 ± 0.8 with a range of 1.7 to 5.7.

VII.2.1.3 SUMMARY

1. The mean values were similar for all echocardiographic measures in both the symptomatic and asymptomatic patients.
2. Although the degree of LV dilatation was the same in the two groups (6.9 ± 1.1cm versus 6.8 ± 0.9cm), the incidence of marked LV dilatation (DED > 8.0cm) was higher in the symptomatic group (16% versus 7%).
3. An end systolic diameter of > 5.5cm was 3.5 times more common in the symptomatic group (25% versus 7%) and included 4 of the 5 symptomatic patients with a DED > 8.0cm.
4. Fractional shortening as a measure of LV systolic performance was similar in the two groups although 6/28 (21%) symptomatic patients compared to only 1/28 (4%) had a depressed FS ≤ 25.
5. A peak systolic wall stress in the decompensated range (> 600mmHg) occurred infrequently in both groups (3 symptomatic and 2 asymptomatic patients).
6. Virtually identical numbers of patients in each group (11/28 symptomatic and 10/28 asymptomatic) had significant LV hypertrophy as assessed by an echocardiographic CSA > 30.0cm^2).

VII.2.2 EXERCISE EVALUATION:

All 28 asymptomatic patients and 31 of the 32 symptomatic group participated in this part of the study.

The results will be reported in the following way:-

VII.2.2.1 Supine Rest and Exercise Haemodynamic and ERNA responses in Symptomatic and Asymptomatic Aortic Regurgitation (SUPINE EXERCISE).

VII.2.2.2 Erect Rest and Exercise Haemodynamic and ERNA responses in Symptomatic and Asymptomatic Chronic Aortic Regurgitation (ERECT EXERCISE)

VII.2.2.3 Comparison of the Effects of Isometric and Supine Bicycle Exercise on Left Ventricular Performance in Symptomatic and Asymptomatic Aortic Regurgitation (ISOMETRIC EXERCISE).

VII.2.2.4 Graded Equivalent Workload (EWL) Supine Exercise responses in Symptomatic and Asymptomatic Patients (EWL SUPINE EXERCISE).

VII.2.2.O NORMAL VALUES

Five normal healthy volunteers performed supine bicycle exercise to exhaustion and serve as controls for this study. In addition to resting and peak exercise values, mean values are also given for levels 1, 2 and 3 of exercise. The results are summarised in Table 7.4 (overleaf).

Table 7.4: NORMAL RESTING AND PEAK EXERCISE RADIONUCLIDE DATA:

	EF		PFR		ADFR		WORK
	R	P.Ex	R	P.Ex	R	P.Ex	k-pm/min
1	63	77	3.41	5.49	1.43	2.10	1050
2	67	69	3.50	4.76	1.26	2.49	600
3	64	86	2.51	7.33	0.84	3.92	1050
4	61	84	2.70	8.34	1.60	3.96	1050
5	60	81	2.70	6.85	1.07	3.39	750
Mean	63	79	2.96	6.55	1.24	3.17	900
±SD	3	7	0.46	1.43	0.30	0.84	212
LEVEL 1		65±6		3.97±0.29		1.70±0.36	
LEVEL 2		67±6		4.22±0.67		1.99±0.21	
LEVEL 3		73±5		4.56±0.74		2.38±0.41	

VII.2.2.1 SUPINE EXERCISE

Supine exercise will be discussed under the following subheadings:-

VII.2.2.1A Measurements at rest for the two groups.

VII.2.2.1B Summary of supine rest data.

VII.2.2.1C Peak exercise results for the two groups.

VII.2.2.1D Differences within the symptomatic group defined by exercise LVEF response.

VII.2.2.1E Differences within the asymptomatic group defined by LV functional reserve.

VII.2.2.1F Summary of supine exercise data.

VII.2.2.1A MEASUREMENTS AT REST FOR THE TWO GROUPS:

Symptomatic Group (n=31)

The mean heart rate at rest was normal (82 ± 12/min) but 5 patients had a resting tachycardia. All patients had a widened pulse pressure and the mean SBP was elevated at 157 ± 18mmHg. The group mean resting cardiac index was normal (3.2 ± 0.7 L/min/M^2) but 5 patients (16%) had a depressed index (range 1.8 to 2.4 L/min/M^2). The mean resting PCWP was elevated at 17 ± 8mmHg with a wide range of 5 to 43mmHg. One third (11 patients) had normal resting

measurements (mean 11 ± 3mmHg). The mean LVEF was in the normal range at 57 ± 12% but ranged from 33 to 78%. Nine patients (29%) had a reduced resting LVEF (mean 41 ± 6%). Three of the five patients with a reduced cardiac index were in this subset, including the 2 patients with markedly reduced values of 1.8 and 1.9 L/min/M^2 respectively. All but two also had an elevated resting PCWP (mean 25 ± 12mmHg).

The mean PFR was significantly reduced at 2.13 ± 0.72 EDV/sec (normal controls 2.96 ± 0.40 EDV/sec), although the ADFR of 1.14 ± 0.34 EDV/sec was only marginally lower than normal controls (1.24 ± 0.30 EDV/sec). However, both these measures of diastolic filling were similar to those of the asymptomatic group (vide infra).

Asymptomatic Group (n = 28)

The mean values for the haemodynamic measurements at rest are similar to those of the symptomatic group (see table 7.5), with SBP being the only significantly different variable (137 ± 15 versus 157 ± 18mmHg, $p < 0.01$). However, none had a reduced resting cardiac index and a slightly higher percentage (43 versus 35%) had a normal resting PCWP.

The LVEF at rest was higher than in the symptomatic group (62 ± 8 versus 57 ± 12%, p = NS) with a range of 40 to 73%. Only 2 patients (7% compared to 29% in the symptomatic group) had a reduced LVEF of <50%. However, both these patients had normal cardiac indexes (3.9 and 4.1 L/min/M^2) and PCW pressures (13 and 15mmHg).

The PFR was marginally higher than in the symptomatic patients (2.22 ± 0.73 versus 2.13 ± 0.72 EDV/sec, p = NS), but still

significantly lower than in the normal controls (2.96 ± 0.46 EDV/sec, p <0.01). The ADFR was marginally higher than in the group with symptoms (1.19 ± 0.39 versus 1.14 ± 0.34 EDV/sec, p = NS) and only slightly lower than controls (1.24 ± 0.30 EDV/sec, p = NS).

Table 7.5: SUPINE HAEMODYNAMIC AND ERNA MEASUREMENTS AT REST

SYMPTOMATIC (n = 31)								ASYMPTOMATIC (n = 28)							
PT	HR	SBP	CI	SV1	W	EF	PFR	ADFR	PT	HR	SBP	CI	SV1	W	EF	PFR	ADFR
MA	75	165	2.5	34	16	57	1.82	0.99	*SA	78	150	3.5	45	13	65	2.46	1.11
FA	68	170	2.3	34	23	67	3.05	1.10	LA	70	165	2.9	41	16	63	1.82	1.17
RA	77	180	4.5	59	10	58	1.36	0.97	SA	70	170	3.0	43	12	62	1.89	0.91
MB	75	190	3.5	46	36	42	1.48	0.79	*MB	72	150	2.8	39	21	64	1.91	1.03
BB	78	180	3.0	39	16	65	1.90	1.19	*SC	74	140	3.1	42	19	71	2.15	1.16
RC	75	170	2.3	30	16	44	0.97	0.51	*AC	90	160	3.1	34	16	55	3.35	1.60
DD	68	160	3.5	51	20	78	2.69	1.34	GD	95	160	4.1	43	24	54	1.88	1.20
MdV	80	170	3.7	46	19	72	2.37	1.50	DD	76	170	2.9	38	20	61	2.29	1.03
EG	100	170	3.4	34	17	41	2.10	0.99	HH	70	160	3.4	49	18	62	1.72	1.01
KG	100	170	2.8	28	25	59	3.39	1.85	*PJ	90	140	3.9	43	13	59	2.19	1.35
MH	84	190	3.1	37	-	43	2.02	0.95	*JJ	74	160	3.8	51	21	71	2.12	1.16
BH	86	160	-	-	-	50	2.87	1.35	KK	100	160	4.0	49	17	62	2.71	1.59
EJ	82	180	3.3	41	23	62	1.81	1.21	*GM	70	150	2.7	39	13	72	2.23	1.27
JL	80	130	3.4	43	20	42	2.59	1.08	PM	64	180	3.5	55	15	58	1.47	0.93
*NL	120	150	3.4	29	16	33	0.86	0.22	*FN	105	170	4.1	39	15	40	1.53	0.74
*RL	74	140	3.4	47	15	76	2.24	1.08	*NO	72	150	3.5	49	11	65	2.19	1.02
ML	100	150	1.9	19	43	34	1.62	1.06	MP	100	160	3.9	39	15	69	2.41	1.67
*SM	88	150	3.5	40	16	74	-	-	*JP	60	170	3.7	61	18	72	1.93	0.86
HM	70	160	1.8	25	12	40	-	-	IR	88	180	3.5	40	18	60	2.19	1.36
NM	100	130	5.0	50	5	72	4.07	1.87	SR	78	160	2.6	33	30	66	2.42	1.21
HM	78	150	3.0	38	11	57	1.54	0.91	WS	82	150	2.8	34	15	61	2.26	1.25
MN	70	155	3.5	50	16	57	1.97	1.04	TS	68	140	3.0	44	20	53	1.37	0.83
EN	80	130	3.7	46	9	60	2.12	1.31	FT	84	140	4.0	47	18	50	1.97	1.09
*JN	65	130	2.4	37	15	63	-	1.48	VdS	80	160	4.6	57	14	66	2.37	1.25
PN	78	150	3.5	44	12	63	2.31	1.31	LV	70	180	3.7	53	16	65	1.96	1.13
GN	65	140	3.2	50	8	67	1.45	0.94	*CV	66	120	3.0	45	11	63	1.79	0.86
*NP	80	130	3.1	38	10	49	1.54	0.92	*DV	62	140	2.8	44	16	63	2.19	0.77
PP	80	150	3.1	39	18	67	2.53	1.27	*AW	135	140	3.4	25	11	73	5.35	2.73
MvB	80	160	2.5	31	15	51	2.33	1.00									
EvH	80	150	-	-	-	56	-	1.18									
HW	92	150	4.5	49	17	64	2.46	1.51									
MEAN	82	157	3.2	40	17	57	2.13	1.14	MEAN	80	137	3.4	44	17	62	2.22	1.19
±S.D	12	18	0.3	9	8	11	0.72	0.34	±S.D.	16	15	0.6	38	4	8	0.73	0.39

* Group 1A

* Group 2A

HR = Heart Rate
SBP = Systolic blood pressure
CI = Cardiac index
SVI = Stroke volume index
W = Pulmonary capillary wedge pressure
EF = LV ejection fraction
PFR = Peak filling rate
ADFR = Average diastolic filling rate

VII.2.2.IB SUMMARY OF SUPINE REST DATA:

1. Resting haemodynamics were similar in the two groups but in the symptomatic patients:-
   - SBP was higher (157 ± 18 versus 137 ± 15mmHg, $p < 0.01$)
   - 16% of this group had a reduced resting cardiac index versus no asymptomatic patients.
   - 67% had an elevated PCWP versus 57% of the asymptomatic group
2. The mean resting LVEF was marginally lower in the symptomatic group (57 ± 11 versus 62 ± 8%, p = NS) but 29% had a reduced LVEF (<50%) compared to only 7% of the asymptomatic patients.
3. Resting peak and average diastolic filling rates were similar in the two groups with a significantly reduced PFR ($p < 0.01$) but an only marginally reduced ADFR (p = NS).

VII.2.2.1C PEAK EXERCISE RESULTS FOR THE TWO GROUPS:

Symptomatic Group (n = 31)

Work capacity ranged from 150 to 900 kilo-pond meters/minute (k-pm/min) with a mean external workload of 423 ± 158 k-pm/min or approximately 3 levels (9 minutes) of exercise. The limiting symptom in the vast majority (27/31) of patients was shortness of breath, with 8 of this group also complaining of leg fatigue. In only 4 patients(13%) was leg fatigue alone the limiting symptom. No patients complained of chest pain. One patient had a self-limiting run of ventricular tachycardia at peak exercise, otherwise no ectopy was noted on exercise.

Cardiac index increased by a mean of 119% from 3.2 ± 0.7 to 7.0 ± 2.0 $L/min/M^2$. Despite this reasonable effort tolerance and significant increase in cardiac index, PCWP increased markedly

from 17 ± 8 to 30 ± 11mmHg with a range of 15 to 55mmHg, and was abnormal in all but 3 patients (90%). Those 3 patients with a normal exercise PCWP had low resting values of 5,8 and 9mmHg respectively.

The majority (81%) had a signifcant fall in LVEF at peak exercise, with the remaining 6 patients having an equivocal response (no change) and no patient displaying a normal functional reserve. This abnormal LVEF response was also seen in the 3 patients whose PCWP did not rise on exercise. The mean LVEF fell significantly from a resting value of 57 ± 12 to 47 ± 14%, $p < 0.01$). This value was appreciably lower than the exercise LVEF in the asymptomatic group, $p < 0.01$. Both PFR and ADFR increased significantly at peak exercise from 2.13 ± 0.72 to 3.25 ± 1.43 EDV/sec (53%) and 1.14 ± 0.34 to 1.58 ± 0.75 EDV/sec (39%). These peak exercise values are approximately only half of normal controls at similar heart rates (PFR 6.55 ± 1.43 EDV/sec; ADFR 3.17 ± 0.84 EDV/sec).

Asymptomatic Group (n = 28)

The mean maximal workload completed during supine bicycle exercise was significantly higher in this group (698 ± 186 versus 423 ± 158 k-pm/min, $p < 0.01$), with a range of 350 to 1050 k-pm/min. This represents approximately 4.5 levels of exercise or an exercise duration of 13.5 minutes, i.e. 1.5 times that of the symptomatic patients. In sharp contrast to the symptomatic group, exercise in these patients was limited by leg fatigue (24/28 or 86%), and only 6 patients complained of shortness of breath. In only 4 (14%) was the limiting symptom shortness of breath alone. None reported chest pain and one had a self-limiting run of ventricular tachycardia(20 beats) at peak exercise.

Heart rate and systolic blood pressure predictably increased significantly from 80 ± 16/min and 157 ± 15mmHg at rest to 173 ± 20/min and 235 ± 29mmHg at peak exercise. Peak heart rate, but not SBP, was significantly higher than in the symptomatic patients ($p < 0.01$). Cardiac index also increased markedly by an increment of 185% from 3.4 ± 0.6 to 9.7 ± 3.1 L/min/M^2 at peak exercise, being significantly higher than in the symptomatic group ($p < 0.01$).

Table 7.6: SUPINE HAEMODYNAMIC AND ERNA MEASUREMENTS AT PEAK EXERCISE

	SYMPTOMATIC (n = 31)									ASYMPTOMATIC (n = 28)							
PT	HR	SBP	CI	SVI	W	EF	PFR	ADFR	PT	HR	SBP	CI	SVI	W	EF	PFR	ADFR
MA	170	230	6.2	36	38	52	-	-	*SA	200	220	9.0	45	12	65	3.84	2.31
EA	165	300	7.2	44	40	52	3.85	1.36	LA	190	240	11.4	60	15	56	5.65	3.00
RA	180	260	8.5	48	18	50	3.14	1.41	SA	190	230	14.3	75	15	55	5.64	2.77
MB	130	270	5.7	44	50	36	0.48	0.12	*MB	165	230	10.5	64	30	62	4.04	2.40
BB	180	290	7.8	43	28	49	2.08	1.09	*SC	180	200	10.3	57	13	82	5.19	2.57
RC	110	180	3.6	33	23	31	1.31	0.47	*AC	130	210	8.3	64	14	60	5.19	2.51
DD	164	230	10.1	61	28	64	3.93	2.00	GD	190	230	8.9	47	25	43	3.32	1.34
MdV	140	220	6.6	47	55	52	3.82	1.91	DD	180	290	13.0	72	28	52	5.92	2.31
EG	142	220	4.8	34	28	28	2.35	0.89	HH	165	250	9.5	58	17	57	4.07	2.52
KG	130	220	4.8	36	33	49	3.56	1.77	*PJ	172	200	9.6	56	31	43	4.99	2.32
MH	160	280	7.3	46	-	27	2.26	1.23	*JJ	190	220	11.7	62	25	70	3.99	2.07
BH	122	220	-	-	-	38	2.07	0.96	KK	170	250	9.6	56	20	57	5.93	2.62
EJ	170	270	7.1	42	40	45	3.44	1.44	*GM	160	230	8.4	53	15	68	5.48	2.44
JL	130	165	7.2	55	38	37	3.63	1.44	PM	150	230	9.3	62	20	52	3.07	1.29
*NL	170	180	5.3	31	18	29	1.32	0.71	*FN	170	210	7.3	43	25	46	4.05	1.48
*RL	120	200	8.4	70	16	78	4.34	2.13	*NO	140	210	10.1	72	10	63	3.44	1.90
ML	160	240	4.5	28	38	24	2.58	1.12	MP	200	230	9.3	47	28	59	4.04	1.83
*SM	150	200	6.3	42	30	77	-	-	*JP	160	280	10.4	65	17	71	4.07	2.12
HM	148	190	4.1	28	30	28	-	-	IR	195	300	7.6	39	38	43	4.02	2.11
NM	170	190	9.9	58	15	67	6.27	3.46	SR	140	220	7.0	50	30	50	3.68	1.62
HM	175	260	6.2	36	20	36	3.06	-	WS	190	240	5.9	31	18	52	4.64	2.20
MN	180	250	8.1	45	33	36	1.99	1.04	TS	185	210	7.4	40	38	33	2.71	0.75
EN	150	170	7.9	53	15	53	5.56	2.56	FT	190	220	9.8	51	35	36	3.38	1.94
*JN	180	170	7.3	40	48	67	-	2.58	VdS	165	280	13.4	89	17	56	4.53	2.69
PN	144	210	10.2	71	17	51	3.02	1.33	LV	180	300	12.6	70	35	41	3.52	1.92
GN	170	210	11.6	68	15	58	6.01	2.94	*CV	168	210	11.3	67	15	67	5.37	2.62
*NP	150	160	8.4	56	37	46	4.07	1.62	*DV	140	220	8.9	64	15	61	4.15	1.90
PP	130	210	6.2	48	33	52	2.79	1.41	*AW	198	210	6.9	35	15	83	6.33	3.36
*MvB	120	210	4.0	33	35	49	2.88	1.63									
EvH	140	230	-	-	-	38	-	1.54									
HW	160	280	8.9	56	22	58	4.48	2.44									
MEAN	152	223	7.0	46	30	47	3.25	1.58	MEAN	173	235	9.7	57	22	57	4.44	2.18
±SD	21	39	2.0	12	11	14	1.43	0.75	±SD	20	29	3.1	13	8	12	2.11	0.56

* Group 1A

* Group 2A

Despite near-normal exercise capacity (698 ± 186 versus 900 ± 212 k-pm/min in normal controls) and an appropriate increase in cardiac index, PCWP increased from 17 ± 4 to 22 ± 8mmHg (range 12 to 38mmHg), and was abnormal in the majority (64%) of cases. Interestingly, of the 10 patients who had a normal exercise PCWP of <15mmHg (mean 14 ± 2mmHg), 4 patients had an abnormal resting value and decreased their PCWP on exercise. Importantly, 80% of this subset of patients with a normal exercise PCWP also had a near-normal (equivocal) LV functional reserve. The elevation of PCWP on exercise was however appreciably lower than in the symptomatic patients ($p < 0.01$).

The mean LVEF dropped slightly from 62 ± 8% at rest to 57 ± 12% at peak exercise (p = NS), with just over half the patients (53% versus 81% in the symptomatic group) having an abnormal LV functional reserve. In 9 patients the LVEF remained essentially unchanged (equivocal response) and in only 4 patients (14% versus 80% of normal controls) was there a normal LV functional reserve. In contrast to the moderate increase in peak and average diastolic filling rates at peak exercise in the symptomatic group, there was a marked increase in PFR from 2.22 ± 0.73 to 4.44 ± 2.11 EDV/sec ($p < 0.01$) and ADFR from 1.19 ± 0.39 to 2.18 ± 0.56 EDV/sec ($p < 0.01$) in this group of patients. However, this still only represents 68% of the peak exercise values for the normal controls.

VII.2.2.1D DIFFERENCES WITHIN THE SYMPTOMATIC GROUP AS DEFINED BY EXERCISE LVEF RESPONSE:

Outlined above, only 6 patients had a normal or equivocal response (Group 1A), with the majority (25/31) of the symptomatic group having a fall in exercise LVEF of > 5% (Group 1B), It is

interesting to note that this equivocal LVEF response to exercise occurred over a wide range of resting left ventricular ejection fractions and the stratification of the patients into two subgroups based on exercise ejection fraction response is graphically illustrated in Figure 7.1 overleaf.

Rest:

The mean resting haemodynamic and radionuclide measurements for the two groups are summarised in the following table:-

Table 7.7: HAEMODYNAMIC AND RADIONUCLIDE DATA AT REST

	HR	SBP	CI	W	EF	PFR	ADFR
Group 1A	85± 9	143±12	3.1±0.5	15±2	58±16	1.74±0.69	0.94±0.46
Group 1B	81±10	160±17	3.2±0.8	18±9	57±12	2.20±0.72	1.18±0.31

Although resting heart rates were similar, SBP was higher in Group 1B ($P < 0.01$) resulting in a higher resting internal workload (rate-pressure product of 12960 versus 12155). Cardiac index was similar in the two groups, but PCWP was normal in Group 1A (15 ± 2mmHg) and abnormal at rest in Group 1B (18 ± 9mmHg, p = NS). The resting LVEF was also similar. Interestingly, at equal heart rates, both peak and average diastolic filling rates were higher in the Group 1B patients (PFR 2.20 ± 0.72 versus 1.74 ± 0.69 EDV/sec, $p < 0.05$; ADFR 1.18 ± 0.31 versus 0.94 ± 0.46 EDV/sec, $p < 0.05$).

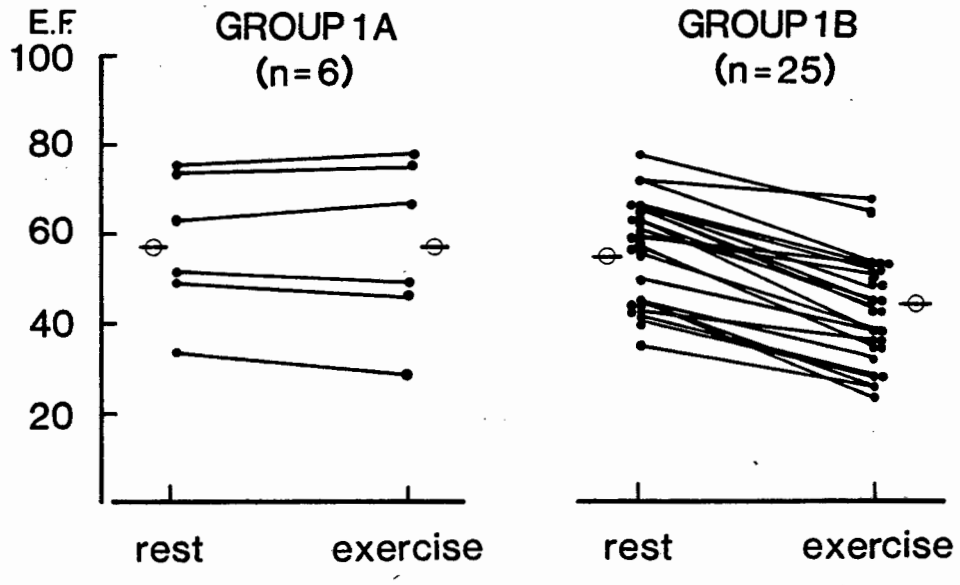
Peak Exercise

The peak exercise results for the two groups is summarised in table 7.8.

Table 7.8: PEAK EXERCISE HAEMODYNAMIC AND RADIONUCLIDE DATA

	HR	SBP	CI	W	EF	PFR	ADFR
Group 1A	148±25	187±20	6.6±1.8	31±12	58±20	3.15±1.38	1.73±0.71
Group 1B	148±35	232±38	7.2±2.1	30±11	44±12	3.26±1.44	1.54±0.78

Figure 7.1: SUPINE REST AND EXERCISE EJECTION FRACTION - SYMPTOMATIC:



Rather surprisingly, maximum workload completed was appreciably higher in the Group 1B patients (442 ± 168 versus 342 ± 66k-pm/min, p <0.05). Heart rate increased to the same peak value but SBP was significantly lower in the Group 1A patients (187 ±20 versus 232 ± 38mmHg, P <0.01). In contrast to the similar resting cardiac indexes, peak exercise cardiac index was marginally higher in Group 1B patients (p = NS) but the PCWP at peak exercise were identical. It is important to note however, that the peak exercise values for the Group 1B patients were generally at a significantly higher external workload.

As illustrated in Figure 7.1, there was an obvious decrease in LVEF from 57 ±12% at rest to 44± 12% at peak exercise in the Group 1B patients, p <0.01. Forty percent(40%) of this group had a markedly reduced peak exercise LVEF of <40% with a range of 24 to 38%. Although PFR was slightly higher at peak exercise in Group 1B patients, p = NS, ADFR was higher in Group 1A, p <0.05 (in contrast to the values at rest). There was a highly significant

difference in the incremental increase of both PFR (81% versus 48% in Group 1B) and ADFR (84% versus 31% in Group 1B).

VII.2.2.1E DIFFERENCES WITHIN THE ASYMPTOMATIC GROUP AS DEFINED BY LV FUNCTIONAL RESERVE

In the asymptomatic patients stratified by LV functional reserve there was a more even distribution with 13 patients having an equivocal or normal response (Group 2A) and 15 patients (54%) having a fall in exercise LVEF of >5%(Group 2B). This subgroup stratification is illustrated in figure 7.2 overleaf.

One again it is evident that the equivocal or normal LVEF response occurred over a wide range of resting values.

Rest:

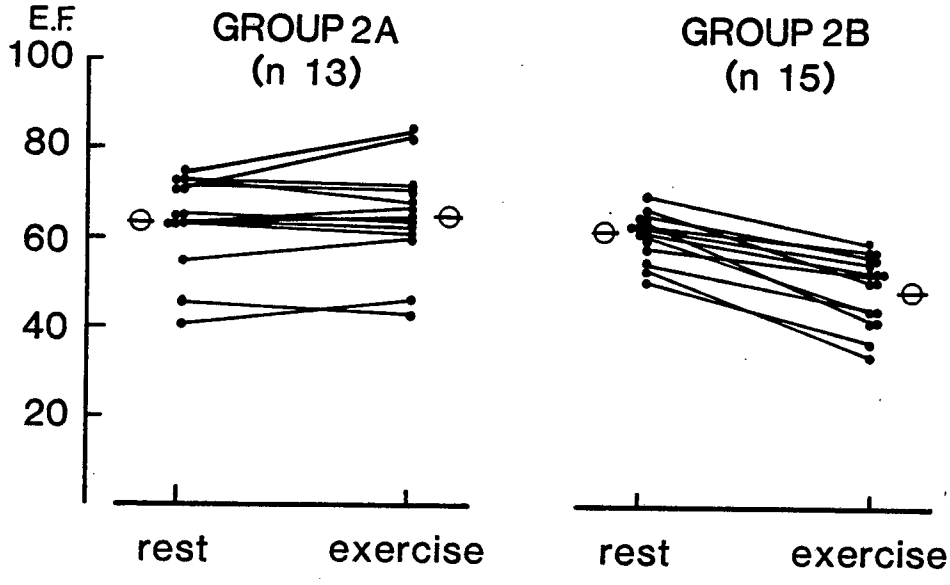
The mean haemodynamic and radionuclide measurements at rest for the 2 subgroups are summarised in the next table.

Table 7.9: HAEMODYNAMIC AND RADIONUCLIDE DATA AT REST

	HR	SBP	CI	W	EF	PFR	ADFR
Group 2A	81±21	151±16	3.3±0.5	15±4	63±10	2.41±0.98	1.20±0.52
Group 2B	80±12	162±13	3.5±0.7	18±4	61± 8	2.05±1.43	1.18±0.23

As in the symptomatic patients, heart rate and cardiac index were similar in the two groups, with a slightly higher SBP in the Group 2B patients and a resultant higher rate-pressure product (12960 versus 12231). The resting PCWP was normal at 15±4mmHg in the Group 2A patients and elevated but not significantly different at 18±4mmHg in Group 2B. These resting PCW pressures are identical to the symptomatic group. Resting LVEF was similar in the two groups, and only marginally higher than the resting values in the symptomatic patients (Group A = 63±10 versus 58±16%; Group B = 61± 8 versus 57±12%).

Figure 7.2: SUPINE REST AND EXERCISE EJECTION FRACTION - ASYMPTOMATIC:



The PFR was slightly higher in the Group 2A patients (2.41 ±0.98 versus 2.05 ±1.43 EDV/sec, p = NS), with similar resting average diastolic filling rates (1.20 ± 0.52 and 1.18 ± 0.23 EDV/sec). The indices of diastolic filling were higher in the asymptomatic subset with a normal exercise LVEF, but Group 1B and Group 2B values were similar.

Peak Exercise

The peak exercise results in the two groups are summarised in the following table:-

Table 7.10: PEAK EXERCISE HAEMODYNAMIC AND RADIONUCLIDE DATA

	HR	SBP	CI	W	EF	PFR	ADFR	WORK
Gr. 2A	167±22	219±21	9.4±1.5	18±7	65±11	4.63±0.85	2.31±0.45	708±212
Gr. 2B	179±17	248±30	9.9±2.5	25±8	49± 8	4.27±1.07	2.06±0.63	690±168

The maximum workload completed was the same in these two subsets of patients. Heart rates were similar (p = NS) but SBP was

appreciably higher in the Group 2B patients (p <0.01) with a resultant higher rate-pressure product (44392 versus 36573). The exercise cardiac index was marginally higher in Group 2B, but the PCWP was significantly higher (25± 8 versus 18± 7mmHg, p <0.05). There was a slight increase in exercise PCWP in the Group 2A patients from 15± 4 to 18±7mmHg which is in sharp contrast to the symptomatic Group 1A subset where a similarly normal resting LV filling pressure of 15± 7mmHg increased markedly to 31±12mmHg.

Figure 7.2 illustrates the obvious decrease in LVEF at peak exercise in the Group 2B patients from a mean of 61±8% to 49±8% which is of a similar magnitude to that occurring in the symptomatic patients. This is significantly lower than the Group 2A subset (p <0.01). However, in sharp contrast to the symptomatic group, only 2 patients (13% versus 40%) had a significantly reduced LVEF < 40%. Both PFR and ADFR were marginally higher in the Group 2A patients (PFR 4.63±0.85 versus 4.27 ±1.07 EDV/sec, ADFR 2.31±0.45 versus 2.06±0.63 EDV/sec) and significantly higher than the corresponding values in the symptomatic patient subsets. Although possibly implying better diastolic filling, it should be noted that higher exercise heart rates in this group could also explain this observation.

VII.2.2.1F SUMMARY OF SUPINE EXERCISE DATA:

1. The maximal external workload completed during supine bicycle exercise was significantly higher in the asymptomatic patients (698 ± 186 versus 423 ± 158k-pm/min, p <0.01) and the limiting symptom was leg fatigue rather than shortness of breath.
2. Exercise haemodynamics were abnormal in both groups with an appreciable elevation in PCWP (symptomatic, 30 ± 11mmHg;

asymptomatic, 22 ± 8mmHg).

3. Most symptomatic patients had an abnormal LVEF response to supine bicycle exercise. In contrast, mean LVEF dropped slightly in the asymptomatic group (62 ± 8% to 57 ± 12%, p = NS), with only half the patients having an abnormal functional reserve. A normal LVEF response occurred over a wide range of resting values.
4. Diastolic function was abnormal in both groups of patients.
5. Thus exercise-induced LV dysfunction is common in asymptomatic patients with chronic severe aortic regurgitation. In addition, these patients are able to tolerate an elevated PCWP on exercise, with leg fatigue being the most common limiting symptom.

VII.2.2.2 ERECT EXERCISE

Erect exercise will be discussed in the same way under the following subheadings:-

VII.2.2.2A Measurements at rest for the two groups.

VII.2.2.2B Summary of erect rest data.

VII.2.2.2C Peak exercise results for the two groups.

VII.2.2.2D Differences within the symptomatic patients defined by exercise LVEF response.

VII.2.2.2E Differences within the asymptomatic group defined by LV functional reserve.

VII.2.2.2F Summary of isometric exercise data.

In general, the responses to upright exercise were directionally similar to those recorded in the supine position. Differences in the magnitude of the changes can be readily explained by predictable haemodynamic changes related to the postural change. It will be noted that not all the patients participated in this

part of the evaluation, with 17 symptomatic patients and 23 of the asymptomatic subgroup performing upright bicycle exercise.

VII.2.2.2A MEASUREMENTS AT REST FOR THE TWO GROUPS

Symptomatic Patients (n = 17)

It should be noted that in only half of this group of patients were the haemodynamics measured in both supine and erect postures. The mean heart rate at rest was 93 ± 7/min with 5 patients having a resting tachycardia (compared to a mean of 82±12 in the supine posture). The mean SBP of 147 ± 13mmHg was 10mmHg lower than in the supine posture. Resting cardiac index was low-normal at 2.7 ± 0.5 L/min/M^2 and appreciably lower than in the supine position (3.2 ± 0.3 L/min/M^2, $P < 0.05$) due to a significantly lower "stroke volume" index of 30 ± 6 versus 40 ± 9ml/M^2, $p < 0.01$ (this measurement reflects forward flow and is not the true stroke volume). Seven patients (41%) had a reduced cardiac index which is in contrast to 16% in the supine posture. Only half of this subset of patients had a depressed cardiac index in both the erect and supine positions.

The mean PCWP at rest was normal at 10±3mmHg compared to 17±8mmHg in the supine position, with only 2 patients (12% versus 65% in the supine posture) having elevated resting values.

The LVEF was normal at 61±17% with a range of 36 to 87%. The five patients with a reduced resting LVEF in the supine position had a similarly reduced LVEF in the upright posture. Three of these 5 patients had a low resting cardiac index, but in contrast to the supine position, only 1 had an elevated PCWP.

Both the PFR of 2.32 ± 0.50 EDV/sec (versus 2.13± 0.72EDV/sec) and the mean ADFR of 1.31± 0.31 EDV/sec (versus 1.14 ± 0.34EDV/sec) are slightly but not significantly higher than in the supine posture. This is probably a function of a higher erect heart rate.

Asymptomatic Group (n = 23)

Although SBP was the same as in the symptomatic group, heart rate (103 ± 10 versus 93 ± 7/min, $p < 0.01$) and cardiac index (3.5 ± 0.5 versus 2.7 ± 0.5 L/min/M^2, $p < 0.01$) were significantly higher with no asymptomatic patient having a reduced resting cardiac index (same as supine posture). In comparison to the symptomatic group, resting PCWP was lower at 7 ±3mmHg (versus 10±3mmHg, $p < 0.01$) with all patients having a normal resting value (compared to only 43% in the supine posture).

The mean LVEF ranged from 51 to 81% (mean 64 ± 8%) and was similar to that of the symptomatic group (61±17%), but in contrast, all patients had a normal resting value (compared to only 93% in the supine posture).

The PFR of 2.66 ± 0.69 EDV/sec (versus 2.32 ± 4.50 EDV/sec) and the ADFR of 1.52 ± 0.44 EDV/sec(versus 1.31±0.31 EDV/sec) are both higher than in the symptomatic group and during the supine posture (PFR 2.22±0.73EDV/sec; ADFR 1.19±0.39EDV/sec.), once again a function of the higher erect heart rate.

VII.2.2.2B SUMMARY OF ERECT REST DATA:

1. The differences at rest compared to the supine posture can be explained by the predictable haemodynamic changes related to posture.
2. Left ventricular ejection fraction was similar in the two

postures and a reduced resting LLVEF was present in both body positions in the same patient.

Table 7.11: ERECT HAEMODYNAMIC AND RADIONUCLIDE DATA AT REST

SYMPTOMATIC (n = 17)									ASYMPTOMATIC (n = 23)								
PT	HR	SBP	CI	SVI	W	EF	PFR	ADFR	PT	HR	SBP	CI	SVI	W	EF	PFR	ADFR
*MA	90	150	2.8	30	22	-	-	-	*SA	104	110	3.3	31	5	54	2.50	0.90
*FA	82	170	2.1	26	15	56	2.99	1.62	*LA	120	160	4.6	38	11	-	-	-
BB	88	150	3.0	35	4	74	2.22	1.47	*SA	80	150	3.0	38	6	60	2.66	1.41
RC	78	160	2.3	30	5	60	1.82	1.03	*MB	92	145	3.1	34	6	63	1.26	0.75
DD	90	150	2.9	32	9	70	2.49	1.42	*SC	120	145	3.2	26	10	74	2.94	1.86
EG	110	150	2.4	22	4	44	2.35	0.87	GD	118	140	3.4	29	11	59	3.09	1.70
MH	84	160	1.9	23	-	41	1.86	0.87	*DD	102	160	4.6	45	10	63	3.14	1.95
EJ	105	160	3.5	34	5	84	3.25	1.96	HH	85	150	3.7	43	6	69	1.89	1.19
JL	90	135	4.0	45	9	43	1.95	1.25	*PJ	112	130	3.3	30	9	51	3.45	1.92
*NL	120	150	2.8	23	10	40	1.76	0.97	*JJ	110	160	4.1	37	6	72	3.40	1.76
RL	75	120	2.9	39	7	85	2.35	1.40	KK	110	160	3.6	33	7	60	2.52	1.56
ML	98	135	2.0	20	30	36	1.66	0.99	FN	108	150	3.3	30	5	53	2.25	1.42
SM	92	150	2.4	26	7	76	-	-	*NO	98	150	3.0	31	2	63	2.87	1.40
HM	110	150	2.9	26	7	59	2.41	1.39	*MP	136	150	3.4	25	5	71	3.20	1.92
*JN	94	130	2.7	29	5	61	2.49	1.48	JP	90	150	3.3	36	7	77	2.51	1.53
*PP	80	130	2.4	31	9	87	3.16	1.62	IR	90	150	3.5	38	8	60	2.41	1.27
*HW	100	150	3.2	32	6	67	2.51	1.27	SR	90	140	3.5	39	10	67	2.07	1.44
									WS	104	140	2.6	25	10	60	-	-
									TS	98	130	3.3	34	8	54	2.10	1.18
									FT	115	150	4.3	38	8	56	2.40	1.64
									*CV	84	120	-	-	5	65	2.25	1.26
									*DV	72	150	3.4	47	3	71	2.41	1.11
									*AW	142	150	2.8	20	4	81	4.61	2.77
MEAN	93	147	2.7	30	10	61	2.32	1.31	MEAN	103	145	3.5	34	7	64	2.66	1.52
±SD	7	13	0.5	6	3	17	0.50	0.31	±SD	10	13	0.5	7	3	8	0.69	0.44
	* GROUP 1A									* GROUP 2A							

VII.2.2.2C PEAK EXERCISE RESULTS FOR THE TWO GROUPS

Symptomatic Group (n = 17)

Because patients were exercised to the maximum work capacity as determined during supine exercise, the mean value of 476 ± 168k-pm/min was similar to the external workload during that posture. Heart rate increased from 93± 7/min at rest to 159±23/min at peak exercise with a similar peak value to that achieved during supine exercise.

Systolic blood pressure rose from 147 ±13 to 218±36mmHg - a similar incremental rise. Cardiac index increased by a mean of 152% from 2.7 ± 0.5 to 6.8± 1.8 L/min/M^2 with the peak value similar to that in the supine posture (7.0 ± 2.0 L/min/M^2). Despite a normal resting PCWP of 10 ±3mmHg, it rose significantly to 22±7mmHg (p <0.01) (range 10 to 30mmHg) at peak exercise, being abnormal in all but 4 patients (76%). The response was similar to that recorded during supine exercise and those with a normal peak exercise PCWP all had a low resting value of < 7mmHg.

Most patients (75%) experienced a significant fall in exercise LVEF from 61±17% at rest to 51±19% at peak exercise. The 4 patients with a normal exercise PCWP all had a significant fall in exercise LVEF. Although PFR and ADFR increased marginally (PFR 2.32±0.50 to 2.94±1.11 EDV/sec; ADFR 1.31±0.31 to 1.48±0.68 EDV/sec), both the peak values and the incremental rise were slightly lower than during supine exercise.

Asymptomatic Group (n = 23)

The work capacity achieved was significantly higher than in the symptomatic group (713±196 versus 476±168k-pm/min, p <0.01). In addition, heart rate (p <0.01), cardiac index (p <0.01) and stroke volume index (p <0.01) were all significantly higher although elevation of PCWP was similar in the two groups. Both heart rate (103±10 to 176±16/min) and SBP (145±13 to 216±25mmHg) increased appreciably and although heart rate was similar to that achieved during supine exercise, SBP was lower with a resultant lower rate-pressure product (38016 versus 40655). Cardiac index increased markedly by 183% from 3.5 ±0.5 to 9.9±3.1 L/min/M^2, similar to the supine posture. PCWP rose from a low-normal mean of 7±3 to

18±7mmHg (range 6 to 30mmHg), and was abnormal in just over half the patients (52% versus 64% during peak supine exercise).

In contrast to the symptomatic group, only 10 patients (43% versus 75%) had an abnormal LV functional reserve with the mean exercise LVEF dropping marginally from 64±8 to 58±11% which is similar to that seen during supine exercise, p = NS. The abnormal response was less common (43% versus 53%) than during supine exercise but in the majority (7/10) the drop in exercise LVEF occurred during both postures. Similar to supine exercise, both PFR (2.66±0.69 to 4.79±2.19 EDV/sec) and ADFR (1.52±0.44 to 2.15±0.82 EDV/sec) increased markedly and was significantly higher (p <0.01) than in the symptomatic group.

Table 7.12: ERECT HAEMODYNAMIC AND ERNA DATA AT PEAK EXERCISE

SYMPTOMATIC (n = 17)									ASYMPTOMATIC (n = 23)							
PT	HR	SBP	CI	SVI	W	EF	PFR	ADFR	PT	HR	SBP	CI	SVI	W	EF	PFR	ADFR
*MA	175	210	5.6	32	28	-	-	-	*SA	170	170	10.1	59	10	64	4.05	1.99
*FA	160	260	8.0	50	30	61	5.09	1.58	*LA	185	230	12.6	68	15	66	5.92	2.67
BB	188	250	9.3	50	25	52	2.27	1.09	*SA	180	220	14.6	81	16	57	6.38	2.84
RC	115	190	3.8	33	13	45	1.46	0.92	*MB	170	230	10.6	62	19	67	5.08	2.41
DD	180	240	8.1	45	26	52	3.94	2.41	*SC	190	210	10.3	54	10	72	5.15	2.54
EG	142	200	5.4	38	12	32	2.12	0.9	GD	190	210	8.9	47	24	46	3.31	1.72
MH	160	260	7.0	43	-	25	1.39	0.67	*DD	180	270	13.2	73	25	60	5.80	3.04
EJ	174	260	6.6	38	31	62	3.85	1.62	HH	170	250	9.8	58	15	52	4.14	2.20
JH	140	190	8.7	62	20	30	2.62	1.14	*PJ	170	180	11.0	65	29	50	4.91	2.07
*NL	165	180	5.5	33	18	39	2.69	0.89	*JJ	180	210	12.3	68	18	72	5.69	2.14
FN	170	210	6.9	41	16	43	2.36	0.88	KK	170	220	9.9	58	15	55	4.70	2.66
RL	130	190	8.4	65	10	70	-	-	*NO	160	210	10.4	65	6	61	2.29	1.43
ML	160	220	4.6	29	30	26	2.20	1.07	*MP	200	210	9.3	46	22	-	-	-
SM	175	220	6.1	35	26	69	-	-	JP	160	270	10.1	63	13	70	6.44	2.91
MN	190	270	5.8	30	21	35	-	-	IR	165	240	8.9	54	25	52	4.86	2.48
JN	170	150	6.2	36	28	68	4.25	2.89	SR	145	220	7.3	51	25	56	3.64	1.60
*PP	115	180	6.2	54	20	90	3.00	1.89	WS	194	200	6.6	34	12	35	-	0.66
HW	160	240	10.5	66	14	53	3.37	2.17	TS	182	200	7.2	39	30	48	2.92	0.24
									FT	188	190	10.8	57	25	45	3.81	2.13
									*CV	180	220	-	-	15	63	6.03	2.98
									*DV	140	190	10.6	76	13	70	4.74	2.01
									*AW	200	200	6.4	32	12	77	8.27	3.68
MEAN	159	218	6.8	43	22	51	2.94	1.48	MEAN	176	216	9.9	57	18	58	4.79	2.15
±SD	23	36	1.8	12	7	19	1.11	0.68	±SD	16	25	3.1	13	7	11	2.19	0.82

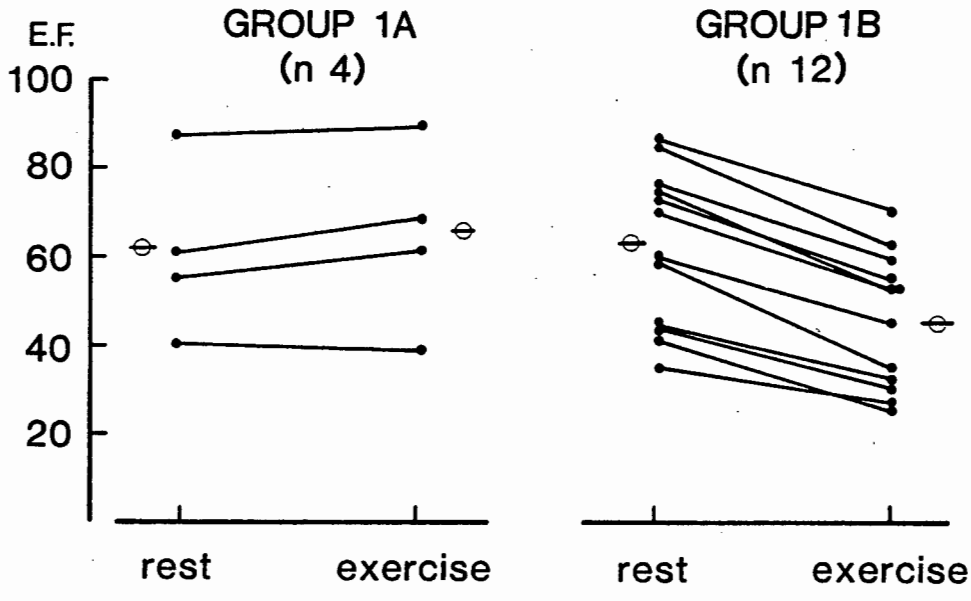
* GROUP 1A

* GROUP 2A

VII.2.2.2D DIFFERENCES WITHIN THE SYMPTOMATIC GROUP DEFINED BY EXERCISE LVEF RESPONSE

As occurred during supine exercise, the majority (75%) had an abnormal peak LVEF response to exercise and constitute Group 1B. Four patients (Group 1A), either increased or did not change their LVEF on exercise. Once again it is evident that the Group 1A response occurred over a wide range of resting LV ejection fractions. The following Figure 7.3 graphically depicts the stratification of the symptomatic subsets.

Figure 7.3: ERECT REST AND EXERCISE EJECTION FRACTION - SYMPTOMATIC



Rest

The resting mean haemodynamic and radionuclide measurements are summarised in the following table:-

Table 7.13: HAEMODYNAMIC AND RADIONUCLIDE DATA AT REST

	HR	SBP	CI	W	EF	PFR	ADFR
Gr. 1A	94±18	145±19	2.5±0.3	6±5	61±20	2.60±0.63	1.42±0.31
Gr. 1B	93±12	148±12	2.8±0.6	8±7	62±17	2.26±0.44	1.27±0.32

In contrast to supine exercise, the resting haemodynamic measurements and radionuclide LVEF and diastolic filling rates were

similar in both subsets of patients. Although resting PFR and ADFR were both significantly higher in the Group 1A patients in the erect posture, this difference was not apparent in the Group 1B patients during the two postures. Similar differences in heart rate occurred and thus cannot explain this observation.

Peak Exercise

The peak exercise mean haemodynamic and radionuclide data for the two subgroups is summarised in Table 7.14.

Table 7.14: PEAK EXERCISE HAEMODYNAMIC AND RADIONUCLIDE DATA

	HR	SBP	CI	W	EF	PFR	ADFR	Ex.Cap
GR. 1A	153±25	193±47	6.5±1.1	24±6	65±21	3.76±1.11	1.81±0.83	413±125
GR. 1B	160±24	228±30	7.0±2.0	21±7	46±16	2.58±0.95	1.34±0.60	500±186

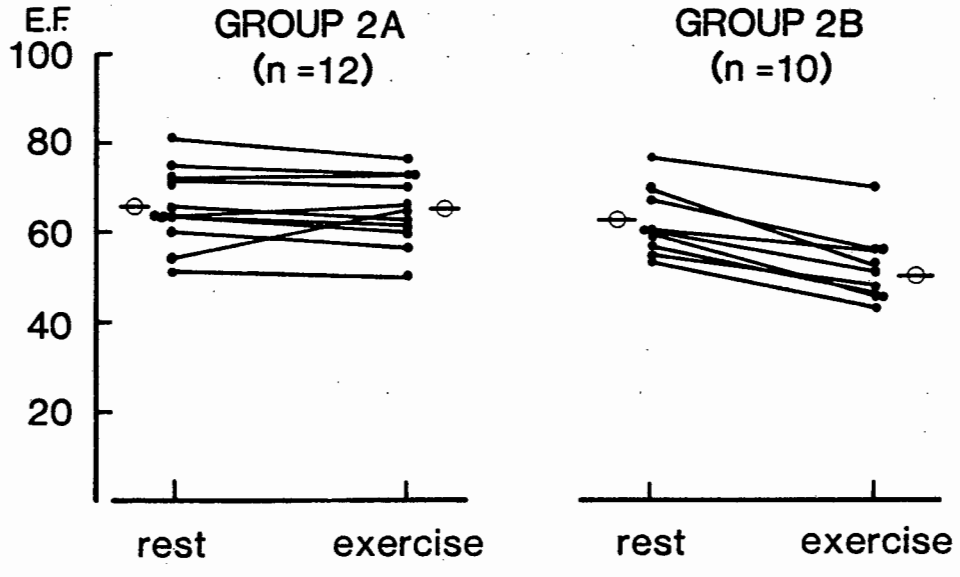
As occurred during supine exercise, peak work capacity was slightly higher in the Group 1B patients (500±186 versus 413±125k-pm/min, p = NS). Although peak heart rates were similar, SBP was significantly higher in the Group 1B patients, p <0.05. Commensurate with the increased work achieved, cardiac index was slightly higher (7.0±2.0 versus 6.5±1.1 L/min/M^2) but PCWP (21±7 and 24±6mmHg) similar in the two subsets. As illustrated in Figure 7.3 Group 1B patients had a marked decrease in exercise LVEF (p <0.05), with 42% of this subset having a significantly reduced value of <40% (range 25 to 35%).

As was evident at rest, PFR (3.76±1.11 versus 2.58±0.95 EDV/sec, p <0.01) and ADFR (1.81±0.83 versus 1.34±0.60 EDV/sec, p = NS) were higher in the Group 1A patients.

VII.2.2.2E DIFFERENCES WITHIN THE ASYMPTOMATIC GROUP DEFINED BY LV FUNCTIONAL RESERVE

As occurred during supine exercise, patient stratification by means of LV functional reserve in asymptomatic aortic regurgitation resulted in a more even distribution of patients, with 12 patients (55%) having a normal or equivocal response (Group 2A) and 10 patients (45%) having a fall in peak LVEF of >5% (Group 2B). This is graphically illustrated in Figure 7.4.

Figure 7.4: ERECT REST AND EXERCISE EJECTION FRACTION - ASYMPTOMATIC



It is again evident that a normal LV functional reserve occurred over a wide range of resting LV ejection fractions with a range of 51 to 81%.

Rest

The mean haemodynamic and ERNA data at rest are summarised in the following table:-

Table 7.15: REST HAEMODYNAMIC AND ERNA DATA

	HR	SBP	CI	W	EF	PFR	ADFR
Gr. 2A	104±21	143±15	3.4±0.5	6±3	66±9	2.89±0.81	1.58±0.56
Gr. 2B	101±12	146± 8	3.5±0.4	8±2	62±7	2.36±0.35	1.44±0.19

The resting haemodynamic and LVEF measurements were similar in the two subsets of patients with resting heart rate higher, SBP lower and PCWP approximately half that in the supine posture where Group 2B patients had an abnormal resting LV filling pressure of 18±4mmHg (compared to 8±2mmHg in the erect posture).

In comparison to the symptomatic subgroup with a normal exercise LVEF, resting heart and cardiac index were higher in the erect posture. Resting PCWP was identical in the two groups. A resting LVEF of 66±9% (versus 61 ± 20%) was marginally higher in the Group 2A asymptomatic subset. As was evident during the supine posture, both PFR (2.89 ± 0.89 versus 2.36±0.35 EDV/sec, p = NS), and ADFR (1.58 ±0.56 versus 1.44±0.19 EDV/sec, p = NS) were only marginally higher in the Group 2A patients. The higher absolute values in both Groups 2A and 2B in the erect posture are related to a higher resting heart rate (see Table 7.9).

Peak Exercise

The peak exercise results in the two groups are summarised in the following table:-

Table 7.16: PEAK EXERCISE HAEMODYNAMIC AND ERNA DATA

	HR	SBP	CI	W	EF	PFR	ADFR
Gr. 2A	175±15	212±26	11.1±2.1	16±6	65±7	5.36±1.43	2.48±0.60
Gr. 2B	173±15	221±25	8.6±1.5	20±6	50±9	4.02±1.20	1.75±0.90

In comparison to supine exercise, maximum work achieved was slightly higher in Group 2A (775±195 versus 665±180k-pm/min, p = NS) with a resultant higher cardiac index (11.1±2.1 versus 8.6±1.5 $L/min/M^2$, p <0.01). However, peak PCWP was lower but nevertheless marginally elevated at 16±6mmHg (versus 20±6mmHg in Group 2B, p = NS). In addition, SBP (212±26 versus 221±25mmHg, p = NS) and the rate-pressure product (37100 versus 38233) were lower. Six

patients (46%) in Group 2A had an abnormal exercise PCWP, which is similar to the number during supine exercise and appreciably lower than the percentage of Group 2B patients with abnormal exercise PCWP during both supine (83%) and erect exercise (60%). Figure 7.4 illustrates the significant decrease in LVEF from 62±7% at rest to 50±9% at peak exercise in Group 2B. This ejection fraction response is significantly different to that of the Group 2A subset ($p < 0.01$). The incremental drop is approximately the same as occurred during supine exercise. The mean value was slightly higher than in the symptomatic subset (50±9 versus 46±16%). In contrast however, only 1 patient (10% versus 42% in the symptomatic group) had a markedly reduced peak exercise LVEF of < 40%.

Both PFR and ADFR rose markedly in the Group 2A patients during peak exercise in the erect posture (PFR 2.8±0.81 to 5.36±1.43 EDV/sec or an 85% increase; ADFR 1.58±0.56 to 2.48±0.60 EDV/sec or a 57% increase), with less impressive incremental rises in the Group 2B patients (PFR 70%; ADFR 22%). Nevertheless, in both subsets, the peak values for both measures of diastolic filling were higher than in the supine posture. Once again, both at rest and, more particularly at peak exercise, these measures of diastolic function appear to correlate best with an abnormal LVEF response to exercise.

Table 7.17 summarises the supine and erect rest and peak exercise haemodynamic and radionuclide data for both the symptomatic and asymptomatic groups of patients.

Table 7.17: SUMMARY OF REST AND EXERCISE HAEMODYNAMIC AND RADIONUCLIDE DATA

	SUPINE n = 31		ERECT n = 17		SUPINE n = 28		ERECT n = 23	
	REST	PEAK	REST	PEAK	REST	PEAK	REST	PEAK
HR	82±12	152±21	93±7	159±23	80±16	173±20	103±10	176±16
SBP	157±18	223±39	147±13	218±36	157±15	235±29	145±13	216±25
CI	3.2± 0.7	7.0± 2.0	2.7± 0.5	6.8± 1.8	3.4± 0.6	9.7± 3.1	3.5± 0.5	9.9± 3.1
FFI (SVI)	40±9	46±12	30±6	43±12	44±8	57±13	34±7	57±13
W	17±8	30±11	10±3	22±7	17±4	22±8	7±3	18±7
EF	57±12	47±14	61±17	51±19	62±8	57±12	64±8	58±11
PFR	2.13± 0.72	3.25± 1.43	2.32± 0.50	2.94± 1.11	2.22± 0.73	4.44± 2.11	2.66± 0.69	4.79± 2.19
ADFR	1.14± 0.34	1.58± 0.75	1.31± 0.31	1.48± 0.68	1.19± 0.39	2.18± 0.56	1.52± 0.44	2.15± 0.82
WORK		423± 158		476± 168		698± 186		713± 196

VII.2.2.2F SUMMARY OF ERECT EXERCISE DATA:

1. The haemodynamic response was directionally similar to that during supine exercise with the same magnitude of change in cardiac index, but a lower SBP and a slightly lower exercise PCWP (symptomatic 22 ± 7 versus 30 ± 11mmHg; asymptomatic 18 ± 7 versus 22 ± 8mmHg).
2. Similar to the supine posture, most symptomatic patients had an abnormal LVEF response to erect bicycle exercise. However, only 39% of the asymptomatic group (versus 53% in the supine posture) had an abnormal functional reserve. Importantly, in the majority of cases the fall in LVEF on exercise occurred during both postures.
3. Diastolic filling rates were reduced in both groups and similar to those obtained during supine exercise.

VII.2.2.3 ISOMETRIC EXERCISE:

This part of the exercise evaluation will compare the effects of isometric handgrip and supine bicycle exercise on LV performance in

symptomatic and asymptomatic patients with aortic regurgitation, firstly for the two big groups as a whole and then stratified according to their supine bicycle exercise LV functional reserve.

Twenty four (24) of the symptomatic group and twenty six (26) asymptomatic patients were evaluated using this form of exercise.

VII.2.2.3A Measurements in symptomatic patients.

VII.2.2.3B Measurements in asymptomatic patients.

VII.2.2.3C Differences within the symptomatic group as defined by supine bicycle exercise LVEF response.

VII.2.2.3D Differences within the asymptomatic group as defined by isotonic exercise LV functional reserve.

VII.2.2.3E Summary of isometric exercise data.

The table overleaf (Table 7.18) outlines the haemodynamic and radionuclide data during isometric handgrip exercise for both the symptomatic and asymptomatic groups.

VII.2.2.3A MEASUREMENTS IN SYMPTOMATIC PATIENTS

The following table summarises the mean resting, isometric and isotonic exrcise data in this group of patients (mean ±SD).

Table 7.19: REST, ISOMETRIC AND ISOTONIC EXERCISE DATA IN THE SYMPTOMATIC PATIENTS

	HR	SBP	CI	W	EF	PFR	ADFR
REST	82±12	157±18	3.2±0.7	17±8	57±12	2.13±0.72	1.14±0.34
ISOMETRIC	86±13	170±21	3.2±0.8	20±9	56±13	2.10±0.38	1.18±0.38
ISOTONIC	152±21	223±39	7.0±2.0	30±11	47±14	3.25±1.43	1.58±0.75

During both forms of exercise heart rate, SBP and rate-pressure product increased (isometric 14620; isotonic 33895), but the

increase was much less during handgrip exercise. Although cardiac index and PCWP increased significantly with bicycle exercise (p <0.01), cardiac index remained unchanged and PCWP increased only marginally during isometric exercise (17±8 to 20±9mmHg, p = NS). Similarly, although LVEF fell significantly (57±12 to 47±14%, p <0.01) at peak bicycle exercise, it remained unchanged during handgrip; similar observations were made when evaluating diastolic filling rates during isometric exercise.

Table 7.18: ISOMETRIC EXERCISE HAEMODYNAMIC AND RADIONUCLIDE DATA

SYMPTOMATIC (n = 24)									ASYMPTOMATIC (n = 26)								
PT	HR	SBP	CI	FFI	W	EF	PFR	ADFR	PT	HR	SBP	CI	FFI	W	EF	PFR	ADFR
MA	80	170	2.6	33	19	54	1.50	0.79	*SA	80	140	3.6	45	14	66	3.24	1.62
FA	80	210	2.9	36	28	60	3.13	1.51	LA	85	180	3.2	37	19	63	1.44	0.75
BB	84	200	2.7	33	22	64	1.95	1.35	SA	80	180	3.4	42	15	57	1.67	1.00
RC	70	180	2.6	37	20	46	1.12	0.45	*MB	80	170	3.8	47	25	61	1.93	1.07
DD	68	165	3.5	52	20	80	2.75	1.39	*SC	76	150	3.6	47	21	71	2.18	1.17
MdV	82	190	3.7	45	24	70	2.43	1.52	*AC	90	170	3.6	40	16	52	3.33	1.59
EG	98	170	2.5	25	15	43	1.99	1.02	GD	96	170	4.1	42	27	50	1.93	1.17
KG	100	180	1.9	19	25	59	3.36	1.87	DD	78	175	3.8	49	22	59	2.28	1.14
MH	80	190	2.6	33	-	45	2.38	0.78	HH	70	180	3.3	47	19	61	1.52	0.91
EJ	80	200	3.5	43	28	61	1.83	1.18	*PJ	92	150	3.7	40	13	45	1.98	1.29
JL	85	140	3.8	45	29	40	2.61	1.22	*JJ	75	195	3.8	51	23	73	2.19	1.21
*NL	120	155	3.8	31	18	34	1.07	0.57	KK	100	170	4.3	43	20	60	2.60	1.39
*RL	80	155	3.7	46	13	73	2.11	1.18	*GM	80	155	3.0	37	13	69	2.10	1.28
ML	110	160	1.6	15	50	30	2.12	0.95	*FN	108	180	3.7	34	18	40	1.46	0.91
*SM	96	180	3.4	35	21	72	-	-	*NO	74	160	3.4	46	11	67	2.17	-
NM	110	145	5.5	50	6	72	-	2.01	MP	102	170	4.9	48	15	71	2.24	1.35
HM	84	170	3.3	39	13	54	-	1.03	*JP	72	180	4.3	60	20	68	2.11	1.25
MN	80	170	3.4	43	20	-	1.44	0.92	IR	92	190	3.8	41	21	62	2.35	1.50
EN	80	130	3.7	46	9	60	2.22	1.33	SR	84	165	2.7	32	33	65	2.23	1.25
*JN	65	130	2.6	40	16	62	1.58	-	WS	82	180	2.9	36	17	60	1.80	1.14
PP	78	160	3.0	39	20	63	2.33	1.22	TS	80	160	2.8	35	25	52	1.36	0.85
*MvB	85	165	2.5	30	15	43	1.99	1.01	FT	84	145	3.9	46	22	50	1.69	1.06
EvH	85	180	-	-	-	57	1.69	1.14	VdS	72	180	3.2	44	17	67	2.42	1.12
HW	94	160	4.4	47	15	57	2.49	1.42	*CV	66	125	2.9	44	12	62	1.66	0.81
									*DV	62	150	3.2	52	21	56	1.78	0.68
									*AW	130	150	3.5	27	10	70	4.95	2.58
MEAN	86	170	3.2	37	20	56	2.10	1.18	MEAN	84	166	3.6	43	19	61	2.18	1.21
±SD	13	21	0.8	9	9	13	0.60	0.38	±SD	14	17	0.5	7	5	8	0.74	0.37

* GROUP 1A

* GROUP 2A

VII.2.2.3B MEASUREMENTS IN ASYMPTOMATIC PATIENTS

The following table summarises the mean resting, isometric and bicycle exercise data in the asymptomatic patients (mean ±SD).

Table 7.20: REST, ISOMETRIC AND ISOTONIC EXERCISE DATA IN ASYMPTOMATIC PATIENTS

	HR	SBP	CI	W	EF	PFR	ADFR
REST	80±16	157±15	3.4±0.6	17±4	62±8	2.22±0.73	1.19±0.39
ISOMETRIC	84±14	166±17	3.6±0.5	19±5	61±8	2.18±0.74	1.21±0.37
ISOTONIC	173±20	235±29	9.7±3.1	22±8	57±12	4.44±2.11	2.18±0.56

As was seen in symptomatic patients, heart rate, SBP and rate-pressure product increased but to a lesser degree than during supine bicycle exercise. Cardiac index and PCWP were only marginally higher than the resting values (p = NS). The radionuclide measurements of LVEF, PFR and ADFR were similar to the resting values (p = NS), which is in sharp contrast to the results during isotonic exercise.

When compared to the isometric exercise response in the symptomatic patients, heart rate, SBP and PCWP were similar, with caridac index, LVEF and diastolic filling rates marginally higher.

VII.2.2.3C DIFFERENCES WITHIN THE SYMPTOMATIC GROUP AS DEFINED BY SUPINE BICYCLE EXERCISE LVEF RESPONSE

Group 1A: (n = 6)

This is the subset of patients with a normal or equivocal LVEF response to supine bicycle exercise. The mean resting, isometric and isotonic exercise results are summarised in table 7.21 (mean ±SD).

Table 7.21: REST, ISOMETRIC AND ISOTONIC EXERCISE DATA IN GROUP IA SYMPTOMATIC PATIENTS

	HR	SBP	CI	W	EF	PFR	ADFR
REST	85±9	143±12	3.1±0.5	15±2	58±16	1.74±0.69	0.94±0.46
ISOMETRIC	89±20	157±18	3.2±0.6	17±3	57±18	1.69±0.47	0.92±0.31
ISOTONIC	148±25	187±20	6.6±1.8	31±12	58±20	3.15±1.38	1.73±0.70

There is a marginal increase in heart rate during isometric exercise with a moderate increase in SBP (p = NS) and thus rate-pressure product (13973 versus 12155 at rest). Cardiac index was similar to the resting value, with a slight elevation of PCWP (17±3mmHg, p = NS). LVEF remained unchanged with PFR and ADFR similarly altering little from the resting values. However, 1 patients (MvB) had a significant fall in isometric LVEF from 51 to 43% which is in sharp contrast to his response during isotonic exercise (51 to 49%).

Group 1B: (n = 25).

In this subgroup with a significant fall in LVEF during supine bicycle exercise (57±12 to 44±12%), the isometric heart rate is again marginally higher with a moderate increase in SBP and rate-pressure product (14792 versus 12960 at rest). As occurred in the Group 1A patients, cardiac index remained unchanged with a slight increase in PCWP from 18±9mmHg at rest to 21±10mmHg during handgrip (p = NS).

Importantly, although somewhat expected, LVEF remained unchanged (as did diastolic filling rates) with only 2 patients (12%) having a significant fall in LVEF during isometric exercise (F.A. 67 to 60%; H.W. 64 to 57%). Thus this form of stress did not appear to help stratify symptomatic patients with chronic aortic

regurgitation into those with and without an abnormal LVEF response to exercise.

The results in this subset are summarised in Table 7.22 (mean ±SD).

Table 7.22: REST, ISOMETRIC AND ISOTONIC EXERCISE DATA IN GROUP 1B SYMPTOMATIC PATIENTS:

	HR	SBP	CI	W	EF	PFR	ADFR
REST	81±10	160±17	3.2±0.8	18± 9	57±12	2.20±0.72	1.18±0.31
ISOMETRIC	86±12	172±21	3.2±0.9	21±10	56±12	2.20±0.59	1.22±0.38
ISOTONIC	148±35	232±38	7.2±2.1	30±11	44±12	3.26±1.44	1.54±0.78

VII.2.2.3D DIFFERENCES WITHIN THE ASYMPTOMATIC GROUP AS DEFINED BY ISOTONIC EXERCISE LV FUNCTIONAL RESERVE

Group 2A: (n = 13).

The mean resting, isometric and isotonic exercise results are summarised in the table below (mean ±SD).

Table 7.23: REST, ISOMETRIC AND ISOTONIC EXERCISE DATA IN GROUP 2A ASYMPTOMATIC PATIENTS

	HR	SBP	CI	W	EF	PFR	ADFR
REST	81±21	151±16	3.3±0.5	15± 4	63±10	2.41±0.9	1.20±0.52
ISOMETRIC	83±18	160±19	3.5±0.4	16± 6	62±10	2.39±0.94	1.29±0.49
ISOTONIC	167±17	219±21	9.4±1.5	18± 7	65±11	4.63±0.85	2.31±0.45

The haemodynamic and radionuclide responses to isometric exercise in this subset of patients varied little from those in the same symptomatic subgroup, with a marginal increase in heart rate and PCWP, a modest rise in SBP and essentially no change in cardiac index, LVEF and diastolic filling rates. However, 1 patient in this subgroup with normal LV functional reserve during isotonic exercise had a significant fall in LVEF during isometric handgrip (D.V. 63 to 56%).

Group 2B: (n = 15)

The results in this subset of patients are summarised in the table below (mean ±SD).

Table 7.24: REST, ISOMETRIC AND ISOTONIC EXERCISE DATA IN THE GROUP 2B ASYMPTOMATIC GROUP

	HR	SBP	CI	W	EF	PFR	ADFR
REST	80±21	162±13	3.5±0.7	18± 4	61± 8	2.05±1.43	1.18±0.23
ISOMETRIC	85±10	173±11	3.6±0.6	21± 5	60± 6	1.96±0.41	1.13±0.22
ISOTONIC	179±17	248±30	9.9±2.5	25± 8	49± 8	4.27±1.07	2.06±0.63

Once again the effects of handgrip isometric exercise on the haemodynamic and radionuclide variables are similar to the symptomatic subset with a fall in LVEF at peak bicycle exercise. LVEF remained unchanged with only 1 patient having an abnormal LV functional reserve (S.A. 62 to 57%). Although SBP was significantly higher than the resting value ($p < 0.01$), PCWP was only marginally higher (p = NS) and thus this form of LV stress was not a helpful alternative method in the asymptomatic group of patients with chronic severe aortic regurgitation.

VII.2.2.3E SUMMARY OF ISOMETRIC EXERCISE DATA

1. Isometric handgrip exercise had only a minimal effect on the measured haemodynamic and radionuclide variables in both the symptomatic and asymptomatic patients.
2. This form of exercise was not a good alternative method of left ventricular stress in patients with chronic severe aortic regurgitation.

VII.2.2.4 EQUIVALENT WORKLOAD EXERCISE

In an attempt to evaluate the patterns of change in haemodynamic and radionuclide variables during supine exercise in more detail,

the measurements at each of the first 3 levels of exercise for both symptomatic and asymptomatic patients were compared and the mean values obtained are summarised in the following two tables (see Appendix VII, VIII, IX for individual patient details) and discussed under subheadings:-

VII.2.2.4A Level 1

VII.2.2.4B Level 2

VII.2.2.4C Level 3

Table 7.25: SYMPTOMATIC HAEMODYNAMIC AND RADIONUCLIDE DATA

	REST	LEVEL 1	LEVEL 2	LEVEL 3	PEAK
HR	82±12	117±14	133±16	151±18	152±21
SBP	157±18	187±27	205±31	220±36	223±39
CI	3.2±0.7	5.4±1.3	6.1±1.6	7.4±1.8	7.0±2.0
W	17±8	27±11	28±12	27±11	30±11
EF	57±12	51±14	50±15	51±15	47±14
PFR	2.13±0.72	2.64±0.85	3.11±1.09	3.26±1.26	3.25±1.43
ADFR	1.14±0.34	1.42±0.53	1.58±0.66	1.69±0.68	1.58±0.75
	n = 31	n = 31	n = 30	n = 22	

Table 7.26: ASYMPTOMATIC HAEMODYNAMIC AND RADIONUCLIDE DATA

	REST	LEVEL 1	LEVEL 2	LEVEL 3	PEAK
HR	80±16	111±23	125±25	142±25	173±28
SBP	157±15	179±21	192±20	208±25	235±29
CI	3.4±0.6	5.7±0.9	6.6±0.9	7.7±1.2	9.7±3.1
W	17±4	21±7	20±6	21±7	22±8
EF	62±8	58±8	58±10	57±11	57±12
PFR	2.22±0.73	2.91±0.79	3.19±0.90	3.78±0.97	4.44±2.11
ADFR	1.19±0.39	1.54±0.32	1.68±1.29	1.97±0.51	2.18±0.56
	n = 28	n = 28	n = 28	n = 28	

VII.2.2.4A LEVEL 1

Symptomatic Patients (n = 31)

All the haemodynamic variables increased during the first level of supine bicycle exercise, with heart rate rising from 82±12 to 117±14/min (incremental rise 43%, $p < 0.01$), SBP from 157±18 to

187±27mmHg(19%, p <0.01), cardiac index from 3.2±0.7 to 5.4±1.3L/min/M^2 (69%, p <0.01) and PCWP by 59% from 17 to 27mmHg (p <0.01). The exercise LVEF fell slightly from 57 to 51% (p = NS), with only 39% of this group having a normal or equivocal response at this level of exercise. This subset of 12 patients included the 6 patients in Group 1A who had an equivocal or normal response at peak exercise (vida supra). PFR increased appreciably by 25% (p <0.05), with only a marginal increase in ADFR (p = NS).

Asymptomatic Patients (n = 28)

In the same way, the haemodynamic parameters all increased during the first level of exercise in the asymptomatic patients with a similar incremental rise in heart rate of 39% (80±16 to 111±23/min, p <0.01), SBP of 14% (157±15 to 179±21mmHg, p <0.01) and a cardiac index increase of 68% (3.4±0.6 to 5.7±0.9 L/min/M^2, p <0.01). In contrast, there was only a marginal increase in PCWP (p = NS) from 17±4 to 21±7mmHg (compared to a 59% increment in the symptomatic group).

There was a slight decrease in exercise LVEF from 62±8 to 58±8% (p = NS) but 9 patients (32% versus 61% of the symptomatic group) had a significant fall in LVEF (62±4 at rest to 50±11%). This subset of asymptomatic patients had a similar incremental rise in cardiac index (74% versus 68% for the whole group) but a higher mean PCWP (25±8 versus 21±7mmHg) and an appreciably greater incremental rise in PCWP of 39% (versus 24% for the group). Nevertheless, this rise in PCWP remained significantly less than during equivalent exercise in the symptomatic patients (59%). Both PFR and ADFR increased significantly by 31% (PFR 2.22±0.73 to 2.91±0.79 EDV/sec, p <0.01) and 29% (ADFR 1.19±0.39 to 1.54±0.32 EDV/sec, p <0.05)

respectively, which is marginally higher than in the symptomatic group.

VII.2.2.4B LEVEL 2:

The following table summarises the incremental change in haemodynamic and radionuclide variables during the 2nd level of supine bicycle exercise.

Table 7.27: INCREMENTAL CHANGE IN HAEMODYNAMIC AND RADIONUCLIDE DATA (LEVEL 2)

	SYMPTOMATIC	ASYMPTOMATIC
HR	+62%	+56%
SBP	+31%	+22%
CI	+91%	+94%
W	+65%	+18%
EF	-12%	- 6%
PFR	+46%	+44%
ADFR	+39%	+41%

Symptomatic Group (n = 30)

All haemodynamic variables increased significantly ($p < 0.01$) ranging from 31% for SBP (157±18 to 205±31mmHg), through 62% for heart rate (82±12 to 133±16/min) and 65% for PCWP (17±8 to 28±12mmHg) to a 91% increase in cardiac index (3.2±0.7 to 6.1±1.6 $L/min/M^2$). The level 2 exercise LVEF fell appreciably from 57±12% at rest to 50±15% ($p < 0.05$), but was little changed from the level 1 value of 51±19%. The peak and average diastolic filling rates increased significantly by 46% and 39% respectively (PFR 2.13±0.72 to 3.11±1.09 EDV/sec, $p < 0.01$; ADFR 1.14±0.34 to 1.58±0.66EDV/sec, $p < 0.05$).

Nine patients (31%) had an equivocal or normal LV functional reserve at this level of exercise (similar to level 1) and included the 6 patients who form the Group 1A subset. This subgroup of

patients had a similar resting LVEF of 58±15% (versus 56±2%) to the subgroup with a fall in exercise LVEF. Resting cardiac index was marginally higher (3.4 ±0.7 versus 3.1±0.7 L/min/M^2) with a similar incremental rise of 88% and 90% respectively. The PCWP both at rest and level 2 exercise was lower (rest 14±4 versus 18±9mmHg; exercise 23±12 versus 30±11mmHg) but with similar incremental rises of 64% and 66% respectively.

Asymptomatic Group (n = 28)

The incremental rise in heart rate and SBP was slightly lower compared to the symptomatic group with heart rate increasing from 80±16 to 125±25/min (56%, p <0.01) and SBP rising from 157±15 to 192±20 (22%, p <0.01) and a lower rate pressure product (24000 versus 27265). The cardiac index rose from 3.4±0.6 to 6.6±0.9 L/min/M^2 (94%, p <0.01). The marginal increase in PCWP from 17±4mmHg at rest to 20±6mmHg (18%, p = NS) is in sharp contrast to the 65% rise in the symptomatic group. The mean level 2 LVEF remained unchanged at 58±8% compared to the first level, with half the patients(14) having a normal or equivocal response (compared to 31% of the symptomatic group).

Neither resting LVEF (61±10 versus 63±6%), nor the haemodynamic variables of cardiac index (3.4±0.5 versus 3.4±0.7 L/min/M^2) or PCWP (16±4 versus 17±5mmHg) distinguished those with a normal or equivocal response from the subset with a fall in exercise LVEF.

The PFR and ADFR increased by 44% and 41% respectively (p <0.01), which is a similar incremental rise to that in the symptomatic group.

VII.2.2.4C LEVEL 3:

Similar to level 2 exercise, the following table summarises the incremental change from rest in the haemodyamic and radionuclide measurements during the 3rd level (450k-p.m./min) of supine bicycle exercise in both the symptomatic and asymptomatic groups.

Table 7.28: LEVEL 3 INCREMENTAL CHANGE IN HAEMODYNAMIC AND RADIONUCLIDE DATA

	SYMPTOMATIC	ASYMPTOMATIC
HR	+84%	+78%
SBP	+40%	+32%
CI	+131%	+126%
W	+59%	+24%
EF	-11%	-8%
PFR	+53%	+70%
ADFR	+48%	+66%

Symptomatic Group (n = 21)

All haemodynamic measurements increased significantly ($p < 0.01$) ranging from 40% for SBP (157±18 to 220±36mmHg), through 59% for PCWP (17±8 to 27±11mmHg) and 84% for heart rate (82±12 to 151±18/min) to a marked 131% increase in cardiac index (3.2±0.7 to 7.4±1.8 L/min/M^2).

The LVEF fell slightly from 57±12 to 51±15% (-11%, p = NS) but it should be noted that this drop occurred during the first level of exercise, after which it plateaued with a further marginal fall to 47±14% only being recorded at peak exercise.

The PFR and ADFR increased further during this level of exercise, PFR by 46% (2.13±0.72 to 3.26±1.26 EDV/sec, $p < 0.01$) and ADFR by 39% (1.14±0.34 to 1.69±0.68 EDV/sec, $p < 0.01$).

Five patients (24% versus 31% in level 2) had a normal or equivocal LVEF response, and included 4 of the Group 1A subset. The other 16

patients had a significant fall in exercise LVEF from 59±11 to 47±11%, p <0.01. Although resting and level 3 exercise cardiac index was similar in Groups 1A and 1B (resting 3.5±0.9 versus 3.3±0.7 L/min/M^2; exercise 7.3±1.6 versus 7.5±2.0 L/min/M^2), resting PCWP was somewhat lower and in the normal range in the Group 1A patients (13±5 versus 17±9mmHg, p = NS). In addition, resting peak and average diastolic filling rates were marginally higher (PFR 2.39±1.61 versus 2.10±0.50 EDV/sec; ADFR 1.16±2.10 versus 1.11±0.14 EDV/sec) with a significant increase in ADFR of 81% at level 3 exercise in the Group 1A patients implying better overall diastolic function in this subset.

Asymptomatic Patients (n = 28)

As occurred during level 2 exercise, the incremental rise in heart rate and SBP was slightly lower in the asymptomatic group with heart rate increasing by 78% from 80±16 to 142±25/min (p <0.01) and SBP rising by 32% from 157±18mmHg at rest to 208±25mmHg (p <0.01). Cardiac index rose by 126% from 3.4±0.6 to 7.7±1.2 L/min/M^2 (p <0.01) with an insignificant rise in PCWP of 24% from 17±4 to 21±7mmHg (compared to a 59% rise in the symptomatic group). It should again be noted that similar to the symptomatic patients, after an initial increase in PCWP during the first level of exercise, no further increase occurred during successive levels. Similarly, after an initial marginal fall in exercise LVEF, no further drop occurred with the LVEF at level 3 of supine bicycle exercise 57±11% (versus 62±8% at rest).

Twelve patients (43% versus 50% in Level 2) had no significant fall in exercise LVEF, and although resting cardiac index was similar to the Group 2B subset (3.3±0.5 and 3.6±0.6 L/min/M^2), resting PCWP

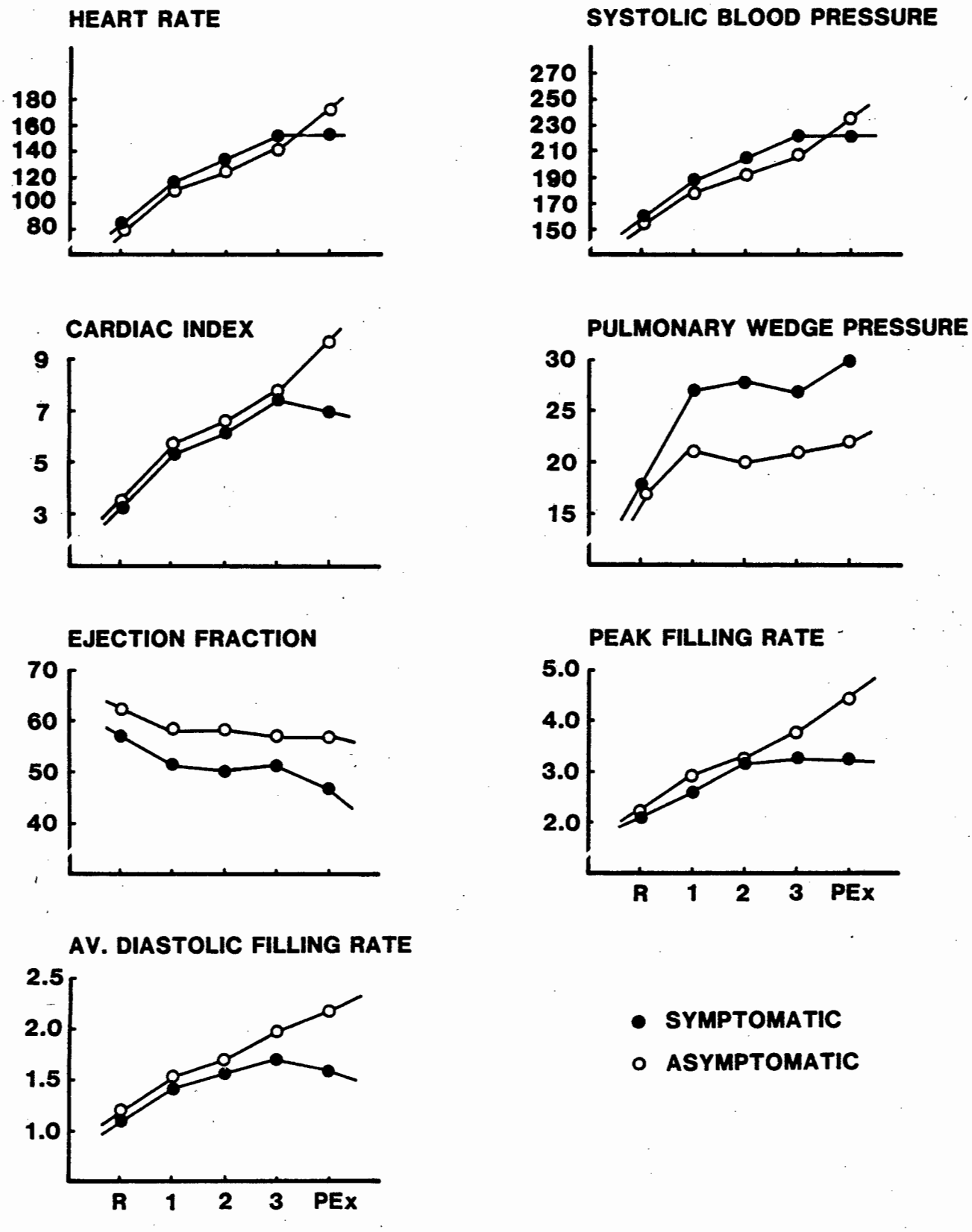
was lower and in the normal range at 15±4mmHg (versus 18±4mmHg). Resting peak and average diastolic filling rates were marginally higher (PFR 2.47±1.01 versus 2.03±0.36 EDV/sec, p = NS; ADFR 1.27±0.55 versus 1.13±0.20 EDV/sec, p = NS), with a much bigger incremental rise in PFR (70%) from 2.22±0.73 EDV/sec at rest to 3.78±0.97 EDV/sec (p <0.01) and ADFR (66%) 1.19±0.39 EDV/sec at rest to 1.97±0.51 EDV/sec (p <0.01). This superior diastolic filling may explain the lower pulmonary capillary wedge pressures, better systolic function and exercise capacity in this group of patients with chronic severe aortic regurgitation.

Figure 7.5 overleaf graphically summarises the pattern of change in the haemodynamic and ERNA variables at each level of supine bicycle exercise in the symptomatic and asymptomatic groups.

VII 2.2.4D SUMMARY OF EQUIVALENT WORKLOAD EXERCISE

1. An appropriate incremental increase in heart rate, SBP and cardiac index was noted in both groups of patients.
2. Whereas PCWP increased marginally during graded supine bicycle exercise in the asymptomatic group (17 ± 4 to 21 ± 7mmHg, p = NS), wedge pressure increased significantly (17 ± 8 to 27 ± 11mmHg, p < 0.01) and early (during level 1 exercise) in the symptomatic patients and then appeared to plateau.
3. A similar early but non-significant fall in LVEF was noted in both groups of patients, followed by a plateau over the next 2 levels of exercise.
4. At similar exercise heart rates there was better diastolic filling in the asymptomatic patients and this may help to explain the lower PCWP, better systolic function and exercise capacity in this group of patients.

Figure 7.5: PATTERNS OF CHANGE IN HAEMODYNAMIC AND ERNA VARIABLES DURING GRADED SUPINE EXERCISE:



5. Thus the direction and magnitude of change in haemodynamic and radionuclide variables appears maximal early during supine bicycle exercise.

VII.2.3 CARDIAC CATHETERISATION

The cardiac catheterisation data of the two groups of patients is outlined in tables 7.29 and 7.30. All patients had normal coronary angiograms.

VII.2.3.1 SYMPTOMATIC GROUP (n = 32)

Aortic Pressure:

The mean systolic aortic pressure was 145 ± 21mmHg with a range of 110 - 220mmHg. The mean diastolic aortic pressure was 55 ± 12mmHg with a range of 30 - 80mmHg. This value was marginally higher than reports in the literature (50 ± 6mmHg, Mann 1975). Fifteen of the thirty two patients (47%) had an aortic diastolic pressure > 60mmHg, but this was not associated with a higher systemic vascular resistance (18.2 ± 3.0 versus 16.8 ± 3.0 Wood units, p = NS in the other 17 patients). It is however consistent with severe aortic regurgitation as a major determinant of the amount of regurgitation is the pressure difference between the aorta and the left ventricle and not the aortic diastolic pressure alone.

In the subset with an aortic diastolic pressure > 60mmHg, the mean aortic pressure was 94 ± 11mmHg (range 83 to 127mmHg). This was appreciably higher than that recorded in the other subset (79 ± 8, range 67 to 93mmHg, $p < 0.001$). The left ventricular end-diastolic pressures were the same in the two subsets (19 ± 5 versus 19 ±

11mmHg p = NS) and thus the aorta to left ventricular pressure difference in the subset with the higher aortic diastolic pressure was significantly higher (75 ± 15 versus 59 ± 9mmHg, $p < 0.01$).

Pulmonary Capillary Wedge Pressure: (PCWP)

The mean resting supine PCWP was elevated at 16 ± 7mmHg with a range of 9 to 44mmHg. Thirteen of the 32 patients (41%) had abnormal resting values. A reasonably good correlation existed between the PCWP measured at cardiac catheterisation and that measured during the exercise evaluation ($r = +0.72$ vide infra).

Left Ventricular End-diastolic Pressure: (LVEDP)

The mean LVEDP was elevated at 19 ± 8mmHg and ranged from 8 to 40mmHg. It was elevated in twenty one of the 32 patients(66%). There was a good correlation between the PCWP and LVEDP at cardiac catheterisation ($r = +0.76$). Similarly there was a good correlation between the LVEDP at cardiac catheterisation and the resting PCWP at exercise evaluation ($r = +0.74$, vide infra).

Cardiac Index:

The group mean cardiac index was normal (3.21 ± 0.92L/min) with a range of 1.90 to 6.43L/min. Five patients had a reduced cardiac index of < 2.5L/min/m^2 and all these patients had an elevated LVEDP (mean 31mmHg, range 20 to 40mmHg). The correlation between the resting cardiac index obtained by the dye dilution technique at cardiac catheterisation and that obtained by the thermodilution technique during the exercise evaluation was poor ($r = +0.37$).

Left Ventricular End-diastolic Volume Index: (LVEDVI)

The mean EDVI was markedly elevated at 193 ± 63ml/M^2 with all but 2 patients having an EDVI > 110ml/M^2.

Table 7.29: CARDIAC CATHETERISATION DATA (SYMPTOMATIC) n = 32:

PT.	AoP S	AoP D	PCWP	LVEDP	CI	EDVI	ESVI	EF	RF A	RF F	A.R.
M.A.	140	50	14	20	2.78	200	96	52	67		4+
F.A.	140	50	12	16	3.56	202	95	51	48	32	4+
R.A.	150	65	10	8	3.63	188	165	64	65		4+
M.B.	160	50	24	28	3.35	269	152	43	59		4+
B.B.	140	30	12	14	3.25	236	93	59	66	75	4+
R.C.	150	50	18	20	2.42	187	112	40	51		4+
D.D.	170	60	16	26	3.80	229	67	70	70		4+
MdeV	140	30	12	18	2.54	300	146	50	78		3-4+
E.G.	150	50	14	20	3.61	245	109	55	72		4+
K.G.	130	50	20	25	2.27	152	58	61	73		4+
M.H.	140	60	20	36	2.30	189	109	41	60		4+
B.H.	135	55	44	32	1.90	205	113	44	71		3+
E.J.	180	50	9	12	3.01	129	49	61	54	52	4+
J.L.	110	45	20	24	4.42	282	214	23	23		3-4+
N.L.	160	80	22	16	3.73	170	99	41	56		3+
R.L.	133	60	7	8	2.50	92	27	69	35		3+
M.L.	140	65	34	40	1.90	194	133	31	65		4+
S.M.	130	50	11	20	3.02	157	57	63	63		4+
H.M.	180	50	13	16	2.50						3+
N.M.	120	70	4	3	2.70	115	33	69	64		3+
H.M.	140	60	16	12	3.03	196	126	35	53		3-4+
M.N.	130	40	14	16	2.85	237	69	70	77		4+
E.N.	140	60	12	26	3.92	166	69	57	44		3-4+
J.N.	160	90	14	20	4.36	172	70	59	45	37	3-4+
P.N.	140	45	16	20	2.83	212	78	63	76		4+
G.N.	155	60	10	12	3.64	371	121	67	82		3+
N.P.	130	50	15	14	2.52	234	80	65	80		4+
P.P.	150	60	16	28	2.96	99	30	69	39	44	4+
MvB	130	60	13	18	2.91	134	68	48	38		3+
EvH	140	70	12	12	3.25	142	64	54	47		4+
MvW	220	80	14	22	3.61	110	51	54	28		3+
H.W.	135	45.	12	15	5.11	222	89	59	59		4+
MEAN	145	55	16	19	3.21	193	88	54	58		4+
±S.D.	21	12	7	8	0.92	63	9	12	16		

AoP s = systolic aortic pressure

AoP d = diastolic aortic pressure

PCWP = Pulmonary capillary pressure

LVEDP = left ventricular end-diastolic pressure

CI = cardiac index

ESVI = left ventricular end-systolic volume index

EF = ejection fraction

RF A = angiographic regurgitant fraction

RFF = electromagnetic flowmeter regurgitant fraction

AR = angiographic grade of aortic regurgitation

EDVI = left ventricular end-diastolic volume index

Left Ventricular End-systolic Volume Index: (LVESVI)

Twenty eight of the group had an ESVI > 50ml/M^2. The mean ESVI of the group was 88 ± 9ml/M^2.

Left Ventricular Ejection Fraction: (LVEF)

The mean value for the group was within the normal range at 54 ± 12%. Only 28% of cases (9 patients) had an abnormal resting LVEF of <50%.

Regurgitant Fraction:

The mean angiographic regurgitant fraction was 58 ± 16% with a range of 23 to 82%. Sixteen patients had a regurgitant fraction of > 60%. In 4 patients the regurgitant fraction was also measured by an electromagnetic flowmeter with a good correlation (r = +0.82).

Degree of Aortic Regurgitation:

All patients had angiographically severe aortic regurgitation with 22 patients having 4+ aortic regurgitation and 8 having 3+ regurgitation.

VII.2.3.2 ASYMPTOMATIC GROUP: (n = 28)

Aortic Pressure:

The group mean systolic aortic pressure was similar to that of the symptomatic group (146 ± 18mmHg) but the mean diastolic aortic pressure was significantly higher (62 ± 13mmHg, p <0.05). In addition the systemic vascular resistance was appreciably lower (14.8 ± 3.2 Wood units, range 8.0 to 23.1, p < 0.01). As occurred in the symptomatic group, there was no difference in the systemic vascular resistance when the group was stratified according to an

aortic diastolic pressure > 60mmHg (15 ± 2.3 versus 14.6 ± 4.5, p = NS). Eighteen patients (64%) had an aortic diastolic pressure > 60mmHg in contrast to 47% of the symptomatic group.

Nevertheless, this is similarly compatible with haemodynamically severe AR with the same explanation as described in the symptomatic group (vide supra). The subset with an aortic diastolic pressure > 60mmHg had a significantly higher aorta to left ventricular pressure gradient (80 ± 10mmHg, range 63 to 96mmHg, p < 0.01) than that recorded in the subset with the lower diastolic pressure (66 ± 11, range 47 to 81mmHg). As occurred in the symptomatic group LV end-diastolic pressures were the same in both subsets (15 ± 5 versus 15 ± 5, p = NS).

Pulmonary Capillary Wedge Pressure:

In contrast to the elevated resting PCWP in the symptomatic group (16 ± 7mmHg), the asymptomatic patients had a normal mean value of 13 ± 3mmHg (p <0.05) and only 4 patients had values above 15mmHg. A reasonably good correlation existed between the PCWP and LVEDP obtained at catheterisation (r = +0.60). Although in individual patients there was a poor correlation between the PCWP measured at catheterisation and that obtained at the time of the exercise evaluation (r = +0.23), the group ranges were similar.

Left Ventricular End-diastolic Pressure:

The range of LVEDP in this group was 6 to 28mmHg with an upper limit of normal mean value of 15 ± 5mmHg. In contradistinction to the small number of patients with abnormal PCW pressures (4 patients), 13 patients (46%) had abnormal supine LVEDPs with a range of 16 to 28mmHg. Importantly, a reasonable correlation existed between the PCWP at exercise evaluation and the LVEDP

measured at cardiac catheterisation (r = +0.52).

Cardiac Index:

The mean cardiac index was appreciably higher than in the symptomatic group (3.86 ± 0.54 versus 3.20 ± 0.92L/min/m^2, p <0.01). No patients had a reduced cardiac index (< 2.5L/min/m^2). As in the symptomatic group, there was a poor correlation between resting cardiac index obtained by the dye dilution and thermodilution techniques (r = +0.15).

Left Ventricular End-diastolic Volume Index:

The mean LVEDVI was 194±111ml/M^2 which is similar to that in the sypmtomatic group (193±63ml/M^2), with all patients having an LVEDVI > 110ml/M^2.

Left Ventricular End-systolic Volume Index:

The LVESVI ranged from 43 to 164ml/M^2 with a mean of 111±12ml/M^2. This value was significantly higher than that in the symptomatic group (88±9ml/M^2, p <0.01).

Left Ventricular Ejection Fraction:

The mean LVEF in this group was normal at 56 ± 9% with a range of 32 to 71%. Only 5 patients (18%) had a reduced LVEF < 50% in contrast to 9 patients in the symptomatic group.

Regurgitant Fraction:

The angiographic regurgitant fraction was lower than in the symptomatic group (p <0.05), ranging from 23 to 81% with a mean value of 49 ± 13%. In contrast to half the patients in the symptomatic group, only 5 patients (18%) had a regurgitant fraction of > 60%. In 8 patients the regurgitant fraction was also measured using the electromagnetic flowmeter technique with 5 out of 8

having a good correlation (mean angiographic 49% vs mean electromagnetic flowmeter 47% r = +0.85).

Degree of Aortic Regurgitation:

Similarly all patients had angiocardiographically defined severe aortic regurgitation with all but 5 patients having 4+ aortic regurgitation. These patients had 3+ regurgitation.

Table 7.30: CARDIAC CATHETERISATION DATA (ASYMPTOMATIC) n = 28

PT.	AoPS	AoPD	PCWP	LVEDP	CI	EDVI	ESVI	EF	RFA	RFF	A.R.
S.A.	155	70	10	14	4.17	162	73	54	30	20	3+
L.A.	140	60	10	10	3.54	244	96	50	50		4+
S.A.	115	35	14	15	3.21	225	119	47	50		4+
M.B.	160	70	14	10	4.70	-	-	-	-		3-4+
S.C.	115	65	10	10	3.96	137	60	55	44	25	3+
A.C.	150	55	15	14	3.09	304	96	68	81		4+
G.D.	170	80	15	22	3.76	142	62	55	37		4+
D.D.	135	65	14	20	3.97	196	76	60	54		4+
H.H.	140	45	11	16	3.36	166	68	59	47		3-4+
P.J.	140	60	11	14	3.36	136	60	55	52		4+
J.J.	170	80	14	18	4.31	220	70	67	61		3-4+
K.K.	130	40	15	14	5.41	200	63	69	58		4+
G.M.	125	55	9	8	4.44	140	61	56	23		3+
P.M.	160	50	8	6	3.06	189	80	56	65		3-4+
F.N.	180	60	16	16	4.20	237	133	44	60	60	4+
N.O.	145	70	12	10	3.88	155	66	57	48		4+
M.P.	160	75	13	12	4.13	175	82	52	53	61	4+
J.P.	160	65	12	22	3.79	152	58	61	28	25	3-4+
I.R.	160	60	20	28	3.40	233	156	32	48	31	4+
S.R.	140	50	16	22	3.44	161	45	71	58	50	4+
W.S.	160	70	9	12	4.51	183	72	60	46		4+
T.S.	125	55	10	16	3.92	258	135	46	54		4+
A.T.	140	55	13	14	3.67	252	99	61	74		4+
Sv/dS	150	60	9	20	3.70	233	108	53	52		3+
L.V.	150	50	13	20	3.55	267	164	38	46		4+
C.V.	105	60	10	12	3.25	135	43	68	36		3+
D.V.	155	90	19	16	3.99	165	73	55	28		3-4+
A.W.	130	70	11	12	6.42	119	54	53	28		4+
MEAN	146	62	13	15	3.86	194	111	56	49		4+
±SD	18	13	3	5	0.54	47	12	9	13		

VII 2.3.3 SUMMARY

1. The mean aortic diastolic pressure was higher than the reported literature with 47% of the symptomatic patients and 64% of the

asymptomatic group having an aortic diastolic pressure > 60mmHg. However, as explained, this finding is nevertheless compatible with haemodynamically severe chronic aortic regurgitation.

2. A moderately good correlation was found between the LVEDP at cardiac catheterisation and the resting PCWP measured with a Swan-Ganz catheter at the exercise evaluation (symptomatic group r = 0.74, asymptomatic group r = 0.52).
3. A poor correlation excisted between the cardiac index measured by the dye dilution technique at cardiac catheterisation and by thermodilution at the exercise study.
4. The EDVI was significantly increased in both groups (symptomatic 193 ± 63, asymptomatic 194 ± 111ml/m^2.
5. The LVEF determined by angiography and by ERNA were similar in the two groups.
6. Angiographic severe aortic regurgitation and normal coronary angiography was present in all patients.

VII.3.0 EARLY POSTOPERATIVE EVALUATION:

Twenty-two(22) symptomatic patients underwent aortic valve replacement. The choice of prosthetic heart valve was influenced by the ability of the patient to take anticoagulant therapy and not by the age of the patient, as the majority of our patients undergoing aortic valve replacement for chronic severe aortic regurgitation are in the younger age group < 40 years (mean 33 ± 14 years), where bioprostheses are contraindicated because of premature degeneration. The final decision on prosthesis choice was at the discretion of the surgeon.

In only twelve patients were mechanical devices inserted, using the

St Jude Medical tilting disc pyrolite prosthesis. Three patients had size 23mm, 7 patients size 25mm and 2 patients size 27mm aortic valve replacements.

Eleven patients had bioprosthetic devices inserted: 8 Hancock (3 size 23mm, 2 size 25mm, 3 size 27mm) and 3 Mitroflo bovine pericardial valve (size 25mm) replacements.

There were no operative deaths. One patient died suddenly on the 17th postoperative day secondary to poor intra-operative myocardial protection and subsequent severe postoperative left ventricular dysfunction. A second patient died suddenly 2 months after operation and a third died at 6 months of the complications of infective endocarditis. The two late deaths occurred in patients with significant pre-operative cardiomegaly and a DED of 9.7cm and 6.8cm and a DES of 7.7cm and 5.8cm respectively. In addition they had evidence of reduced left ventricular systolic function with a fractional shortening of 21% and 15% and respective resting LVEFs of 42% and 34%. Interestingly, and rather sadly, the second patient (DED 6.8cm, DES 5.8cm, FS 15%, LVEF 34%) had near normalised his echocardiographic dimensions at 6 months postoperatively (DED 6.2cm, DES 4.0cm) and had normal resting systolic function (FS 35%, LVEF 55%).

Sixteen of this group of patients had adequate early postoperative echocardiograms and resting ERNAs performed on the 10th postoperative day. Table 7.31 details these results. The individual pre-operative values are in subscript brackets.

VII.3.1 LV DIMENSIONS

Pre-operatively, all 16 patients had echocardiographic evidence of

LV enlargement; the average LV DED was 7.4 ± 1.1cm. Five patients had marked LV dilatation with an LV DED > 8.0cm (range 8.3 to 9.7cm). The mean LV DES was 5.1 ± 1.1cm with 6 patients having a LV DES > 5.5cm (range 5.5 to 7.7cm).

Aortic valve replacement resulted in a significant early reduction in mean LV DED to 5.8 ± 1.3cm ($p < 0.01$) with a variable response in the 5 patients with marked dilatation - in this subgroup the percentage decrease in DED varied from 6 to 35%. When indexed for body surface area, this value of 5.8 ± 1.3cm falls at the upper limit of normal at 3.4 ± 0.7cm and in the compensated range for chronic aortic regurgitation.

The group mean LV DES similarly decreased but less markedly from 5.1 ± 1.1cm to 4.7 ± 1.4cm, p = NS. However, in 4 of the 6 patients with an LV DES > 5.5cm this dimension increased in the early postoperative period. The value of 4.7 ± 1.4cm, when indexed for body surface area, is 2.8 ± 0.7cm/M^2 which falls into the decompensated range for chronic aortic regurgitation (> 2.6cm/M^2).

VII.3.2 LV MASS AND R/TH RATIO

All but one of this group of patients had significant pre-operative left ventricular hypertrophy as determined by the echocardiographic measurement of cross sectional area (CSA). The mean value was 33 ± 8cm^2 with a range of 19 to 48cm^2.

The mean R/Th ratio of 3.3 ± 0.8, used as an index of the volume to mass ratio, was in the normal range in the majority, with only 3 patients having values of > 4.0 (i.e in the decompensated range implying inadequate LV hypertrophy). Two of these 3 patients had considerable LV dilatation with a DED of 9.7cm and 8.4cm

respectively.

Early postoperatively there was no significant change in CSA (33 ± 8 to 29 ± 7cm^2).

VII.3.3 LV SYSTOLIC PERFORMANCE:

The mean pre-operative fractional shortening (FS) for the group was 31 ± 8% which is in the normal range, signifying compensated chronic aortic regurgitation. However, 5 patients had an abnormally low FS < 25%. Paradoxical septal motion precluded calculation of FS in the early postoperative period.

Pre-operative group mean resting left ventricular ejection fraction (LVEF) as measured by equilibrium radionuclide angiocardiography was at the lower limit of normal (51 ± 13%) and in 6 patients the LVEF was between 40 and 50% and in 2 patients it was considerably reduced to < 40%. There was a uniform but insignificant drop in early postoperative LVEF in all but 5 patients, to a mean value of 44 ± 18%. This phenomenon does not represent a true decrease in contractility, but merely reflects altered loading conditions on the left ventricle.

VII 3.4 SUMMARY OF EARLY POSTOP DATA

1. There was a significant decrease in DED early postop except in the 5 patients with marked LV dilatation where the response was variable.
2. The end-systolic dimension similarly decreased but not in the subset of patients with a DES > 5.5cm.
3. Regression of LV hypertrophy was not seen early following aortic valve replacement.
4. Most patients had a marginal drop in LVEF early postop,

probably reflecting altered loading conditions on the LV rather than reduced contractility.

Table 7.31: EARLY POSTOPERATIVE (10 DAYS) ECHOCARDIOGRAM/ERNA DATA (n = 16)

	ECHOCARDIOGRAM								ERNA
PT	DED	DEDI	DES	DESI	FS	R/Th	WS	CSA	LVEF
MB	7.8	3.9	6.5	3.3	-	3.9	700	28	26
	(9.7)	(4.9)	(7.7)	(3.9)	(21)	(4.4)	(1004)	(37)	(42)
BB	5.4	3.4	4.2	2.6	-	1.3	189	46	50
	(8.3)	(5.3)	(5.0)	(3.2)	(40)	(3.5)	(588)	(36)	(65)
RC	7.0	3.5	6.1	3.1	-	2.9	350	31	31
	(8.4)	(4.2)	(5.5)	(2.8)	(34)	(4.2)	(651)	(29)	(44)
MdV	4.2	2.8	3.4	2.3	-	1.2	149	31	45
	(7.0)	(4.7)	(4.4)	(3.0)	(37)	(2.2)	(306)	(43)	(74)
EG	4.8	3.2	3.6	2.4	-	1.3	180	37	44
	(7.7)	(5.1)	(5.0)	(3.3)	(35)	(3.5)	(560)	(30)	(41)
KG	5.0	2.5	3.8	1.9	-	2.1	271	23	70
	(6.0)	(3.1)	(4.0)	(2.0)	(33)	(1.9)	(300)	(38)	(59)
MH	7.5	3.5	6.5	3.0	-	3.1	438	33	20
	(8.6)	(4.0)	(6.0)	(2.8)	(30)	(2.9)	(401)	(48)	(43)
BH	5.8	3.4	4.6	2.7	-	2.6	343	24	33
	(6.7)	(3.9)	(5.0)	(2.9)	(25)	(3.1)	(475)	(33)	(50)
JL	8.1	5.0	7.2	4.4	-	4.5	518	25	31
	(8.6)	(5.3)	(6.7)	(4.1)	(22)	(3.3)	(430)	(40)	(42)
NL	6.0	3.8	5.0	3.2	-	2.5	325	27	24
	(7.4)	(4.7)	(5.6)	(3.5)	(24)	(3.7)	(592)	(26)	(33)
ML	7.3	4.2	5.9	3.4	-	3.6	511	26	31
	(6.8)	(4.0)	(5.8)	(3.4)	(15)	(4.2)	(595)	(19)	(34)
SM	3.8	2.5	3.0	2.0	-	1.6	190	19	82
	(6.2)	(4.1)	(3.7)	(2.4)	(40)	(3.1)	(465)	(23)	(74)
HM	5.8	3.7	4.8	3.1	-	2.7	375	24	43
	(7.2)	(4.6)	(5.2)	(3.3)	(28)	(3.0)	(450)	(32)	(57)
NP	5.7	3.8	4.0	2.6	-	1.9	343	33	63
	(6.6)	(4.4)	(4.7)	(3.1)	(29)	(2.2)	(330)	(38)	(49)
EvH	4.9	3.0	2.5	1.5	-	1.5	184	33	68
	(6.7)	(4.0)	(4.4)	(2.7)	(34)	(3.9)	(663)	(28)	(52)
MvW	4.3	2.8	3.8	2.5	-	-	-	-	40
	(5.9)	(3.8)	(3.5)	(2.3)	(41)	(2.5)	(435)	(27)	(62)
MEAN	5.8	3.4	4.7	2.8	21	2.5	331	29	44
±S.D	1.3	0.7	1.4	0.7	9	1.0	157	7	18
	(7.4)	(4.4)	(5.1)	(3.0)	(31)	(3.3)	(521)	(33)	(51)
	(1.1)	(0.6)	(1.1)	(0.6)	(8)	(0.8)	(180)	(8)	(13)

( ) = Pre-operative values.

VII.4.0 SIX MONTH POSTOPERATIVE EVALUATION:

Of the 22 symptomatic patients who underwent technically successful aortic valve replacement, 19 patients were re-evaluated at 6 months

postoperatively. This assessment included an evaluation of their clinical status, echocardiographic dimensions and systolic function and exercise testing including haemodynamic monitoring and simultaneous equilibrium radionuclide angiocardiography. Cardiac catheterisation was not performed.

VII.4.1 CLINICAL STATUS:

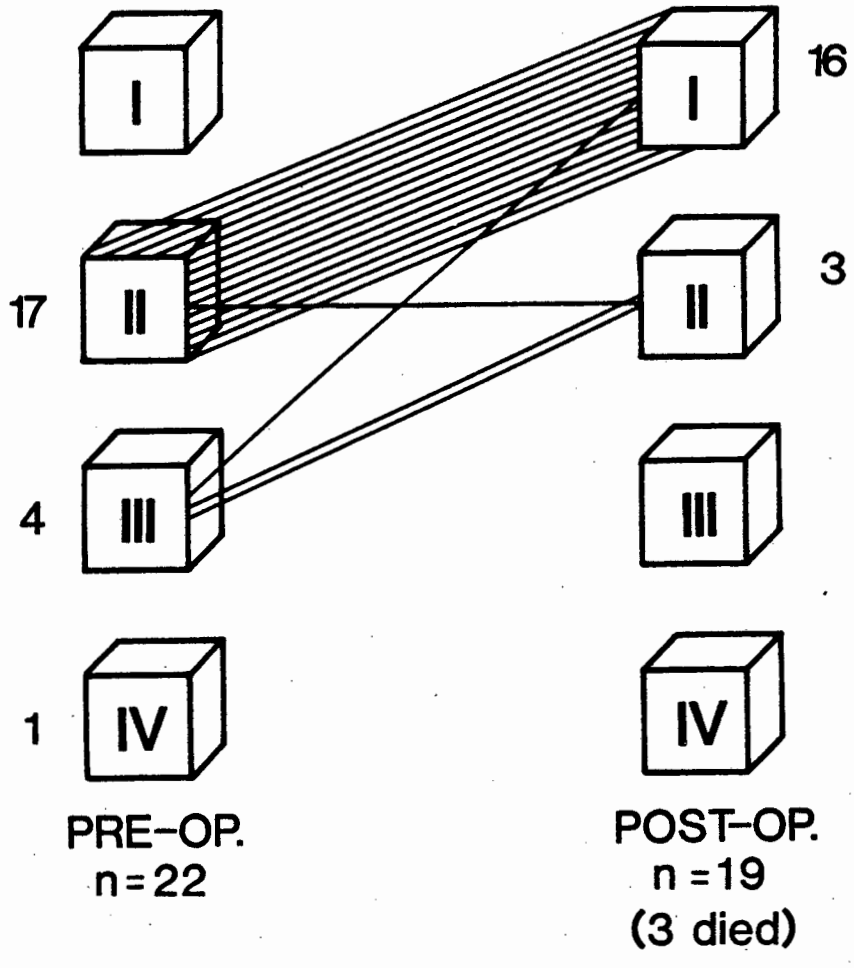
VII.4.1.1 Functional Class:

All but 3 patients were asymptomatic and in NYHA functional Class I at re-assessment. Two of these patients had mild Class IIA symptoms and one patient had a one month history of symptoms of congestive heart failure (Class IV), clinical features of infective endocarditis together with a leaking Hancock aortic valve prosthesis. Thus 84% of the survivors of aortic valve replacement had a normal effort tolerance and 2 of the 3 mildly symptomatic patients had improved by one functional class. One death occurred in each of the groups of patients in pre-operative functional class II, III and IV.

VII.4.1.2 Left Ventricular Hypertrophy on Electrocardiogram:

All patients had significant left ventricular hypertrophy with repolarisation change as assessed by the Sokolow Lyon index with a mean value of 70 $\pm$ 22mm. Following successful aortic valve replacement (AVR) there was a significant decrease in the ECG indices of left ventricular hypertrophy to 52 $\pm$ 15mm and 3 patients had no electrocardiographic evidence of hypertrophy at this assessment. The degree of pre-operative LV hypertrophy was not predictive of normalisation.

Figure 7.6: SUMMARY OF THE POSTOPERATIVE CHANGE IN NYHA FUNCTIONAL CLASS



VII.4.1.3 Cardio-thoracic Ratio:

Seventeen of the 19 patients demonstrated a reduction in cardio-thoracic ratio with the mean value falling from 0.60 ± 0.05 to 0.53 ± 0.05. In 9 patients (47%) there was a normalisation of the cardio-thoracic ratio, and a further 5 patients had a ratio of between 0.50 and 0.55.

In the two patients with no change in cardio-thoracic ratio, one had a normal LV DED on the echocardiogram, but the second had persistent LV dilatation with a DED of 6.9cm. Normalisation of cardio-thoracic ratio was usually (8 out of 9) associated with a

normal LV DED.

VII.4.2 ECHOCARDIOGRAPHY:

The table (7.32) on the following page summarises the effect of aortic valve replacement on LV volume, mass and systolic function at the 6 month postoperative evaluation.

VII.4.2.1 LV Dimensions

The mean pre-operative LV DED was 7.1 ± 0.9cm with a range of 6.0 to 8.6cm. Four patients (22%) had marked LV dilatation with an LV DED > 8.0cm. The mean LV DED fell early postoperatively to 5.8 ± 1.3cm and showed a continued reduction to a value of 5.0 ± 1.0cm at 6 months, $p < 0.01$, i.e. to within the normal range of < 5.3cm for our laboratory. Three out of the 4 patients with severe pre-operative LV dilatation (LVDED > 8.0), had persistent LV dilatation postoperatively (8.3 ± 0.3 to 6.8 ± 0.4cm), confirming that this measure is an indicator of a poor prognosis. However, as previously described, it usually only occurs in a small number of patients (4 in my series).

The mean LV DES decreased marginally from 4.9 ± 0.8 to 4.7 ± 1.4cm early postoperatively, but there was a significant reduction to 3.5 ± 1.1cm at 6 months ($p < 0.01$).

Of the 7 patients with a pre-operative DES > 5.5cm, 2 patients were not evaluated at 6 months following valve replacement surgery. One patient (R.A.) was lost to follow-up and a second patient with marked pre-operative LV dilatation (M.B. - DED 9.7cm, DES 7.7cm) died suddenly 2 months after technically successful aortic valve replacement. Four of the remaining 5 patients (80%) in this subset showed a significant reduction in DES (6.0 ± 0.5 to 4.0 ± 0.6cm, p

<0.01). In this sub-group of patients, 60% (3 of 5) also had marked pre-operative LV enlargement with a LV DED of > 8.0cm, but 2 out of the 3 showed a marked reduction in LV DED (8.6cm to 5.4cm; 8.6cm to 6.4cm) with a significant improvement in LV DES (6.0cm to 3.5cm; 6.7cm to 4.9cm). Appreciating the small sample size, these results are nevertheless at variance with the presently held opinion that a pre-operative LV DES > 5.5cm predicts a poor postoperative outcome.

Table 7.32: SIX MONTH POSTOPERATIVE ECHOCARDIOGRAM: (n = 18)

	DED		DES		FS		R/Th		WS		CSA	
	Pre-	Post	Pre-	Post	Pre-	Post	Pre-	Post	Pre-	Post	Pre-	Post
FA	7.6	5.0	4.9	4.3	35	14	2.5	2.1	456	292	43	23
RC	8.4	7.2	5.5	6.8	34	5	4.2	3.0	651	390	29	32
MdeV	7.0	3.8	4.4	1.9	37	50	2.2	1.3	306	152	43	25
EG	7.7	4.8	5.0	3.2	35	33	3.5	1.6	560	224	30	30
KG	6.0	4.7	4.0	2.7	33	42	1.9	1.6	300	204	38	29
MH	8.6	5.4	6.0	3.5	30	35	2.9	1.9	401	270	48	17
JL	8.6	6.4	6.7	4.9	22	23	3.3	2.9	430	347	40	29
NL	7.4	5.1	5.6	3.6	24	29	3.7	2.6	592	332	26	19
ML	6.8	6.2	5.8	4.0	15	35	4.3	2.8	595	395	19	18
SM	6.2	4.2	3.7	2.5	40	40	3.1	2.3	465	280	23	14
HM	6.0	3.3	3.7	2.3	38	30	3.0	1.7	570	248	22	13
HM	7.2	4.5	5.2	3.2	28	28	3.0	2.1	450	286	32	19
JN	6.2	4.5	4.2	3.5	32	22	3.4	2.2	482	263	20	17
PN	8.0	6.9	5.3	4.3	33	38	3.3	2.9	467	546	35	30
GN	7.0	4.5	5.0	3.0	29	33	2.9	1.9	525	206	31	21
NP	6.6	4.8	4.7	3.2	29	33	2.2	2.4	330	264	38	12
MvB	6.2	4.9	4.6	3.5	25	25	3.1	2.2	465	301	23	21
EvH	6.7	4.4	4.4	3.0	34	32	4.0	1.8	663	220	28	21
MEAN	7.1	5.0	4.9	3.5	31	30	3.1	2.2	484	290	32	22
±SD	0.9	1.0	0.8	1.1	6	5	0.7	1.5	109	90	9	6

VII.4.2.2 LV Mass and R/Th Ratio

As mentioned previously, all but one patient had significant left ventricular hypertrophy as measured by echocardiographic cross sectional area (CSA), with a mean value of 32 ± 9cm^2 and a range of 19 to 48cm^2. There was a significant decrease in cross sectional area at the 6 month postoperative assessment, with a mean value for

the group of 22 ± 6cm^2, p <0.01. Eight patients(44%) normalised their LV mass, and the pre-operative degree of left ventricular hypertrophy measured echocardiographically was not predictive: 50% of the sub-group with severe left ventricular hypertrophy pre-operatively normalised their LV mass postoperatively (mean 36 ± 9 to 17 ± 3cm^2).

The mean pre-operative R/Th ratio was in the normal range at 3.1 ± 0.7 with only 3 patients having inadequate hypertrophy for the degree of LV dilatation and falling in the decompensated range for chronic aortic regurgitation (> 4.0). However, at 6 months postoperatively, all patients had a normal volume to mass ratio as reflected by a mean R/Th of 2.2 ± 1.5, p <0.05.

VII.4.2.3 LV Systolic Performance:

Appreciating that paradoxical septal motion significantly interferes with and invalidates the calculation of fractional shortening (%FS) postoperatively, there was nevertheless no change in FS from a pre-operative value of 31 ± 6% to 30 ± 5% at 6 months postoperatively. In only 4 patients was there an obvious decrease in fractional shortening, with significant paradoxical septal motion seen in 3 of this group. However, fractional shortening appeared to be a poor indicator of postoperative systolic function when compared to equilibrium radionuclide angiocardiography.

VII.4.3 EXERCISE EVALUATION:

The pre- and postoperative exercise evaluation included resting and peak exercise haemodynamic and equilibrium radionuclide angiocardiographic (ERNA) data in both the supine and semi-erect postures, during both isotonic (bicycle) and isometric (handgrip)

exercise. It will be discussed and tabulated in the following way:-

VII.4.3.1 Pre-operative supine rest and peak exercise haemodynamic and ERNA data (PRE-OP SUPINE)

VII.4.3.2 Postoperative supine rest and peak exercise haemodynamic and ERNA data (POSTOP SUPINE)

VII.4.3.3 Pre-operative and postoperative supine exercise haemodynamic and ERNA data at equivalent workload (POSTOP SUPINE EWL).

VII.4.3.4 Pre-operative erect rest and peak exercise haemodynamic and ERNA data (PRE-OP ERECT)

VII.4.3.5 Postoperative erect rest and peak exercise haemodynamic and ERNA data (POSTOP ERECT)

VII.4.3.6 Pre- and postoperative isometric exercise haemodynamic and ERNA data (SUPINE ISOMETRIC)

VII.4.3.1 PRE-OP SUPINE

The results in Table 7.33 have been reported in the symptomatic group as a whole (see sections VII.2.2.1A and VII.2.2.2A) and are summarised as follows:-

1. Resting haemodynamics were similar to the asymptomatic group but in the symptomatic patients:-
   - SBP was higher (157 $\pm$ 18 versus 137 $\pm$ 15mmHg, $p < 0.01$).
   - 16% of this group had a reduced resting cardiac index versus no asymptomatic patients.
   - 67% had an elevated PCWP versus 57% of the asymptomatic group.
2. The mean resting LVEF was 57 $\pm$ 11% but 29% had a reduced LVEF < 50%.
3. Resting peak and average diastolic filling rates were abnormal

with a significantly reduced PFR ($p < 0.01$) but an only marginally reduced ADFR (p = NS).

4. The maximal external workload completed during supine bicycle exercise was 423 ± 158k-pm/min and the limiting symptom was shortness of breath.

5. Exercise haemodynamics were abnormal with a marked elevation in PCWP to 30 ± 11mmHg.

6. Most symptomatic patients had an abnormal LVEF response to supine bicycle exercise. However, in the small subset with a normal LVEF response, this occurred over a wide range of resting values.

7. Diastolic function was abnormal in all patients on exercise.

Table 7.33: PRE-OPERATIVE RESTING AND PEAK EXERCISE HAEMODYNAMIC AND ERNA DATA: (SUPINE ISOTONIC)(n = 19) *Group 1A

	HR		SBP		CI		PCWP		LVEF		PFR		ADFR	
	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex
FA	68	165	170	300	2.3	7.2	23	40	67	52	3.05	3.85	1.10	1.36
*RC	75	110	170	180	2.3	3.6	16	23	44	31	0.97	1.11	0.51	0.47
*MdV	80	140	170	220	3.7	6.6	19	55	72	52	2.37	3.82	1.50	1.91
*EG	100	142	170	220	3.4	4.8	17	28	41	28	2.10	2.35	0.99	0.89
*KG	100	130	170	220	2.8	4.8	25	33	59	49	3.39	3.56	1.85	1.77
MH	84	160	190	280	3.1	7.3	-	-	43	27	2.02	2.26	0.95	1.23
		(150)		(270)		(6.9)				(27)		(2.63)		(1.37)
BH	86	122	160	220	-	-	-	-	50	38	2.87	2.07	1.35	0.96
*JL	80	140	130	175	3.4	8.1	20	30	42	37	2.59	3.63	1.08	1.44
NL	120	170	150	180	3.4	5.3	16	18	33	29	0.86	1.32	0.22	0.71
ML	100	160	150	240	1.9	4.5	43	38	34	24	1.62	2.58	1.06	1.12
SM	88	150	150	200	3.5	6.3	16	30	74	77	-	-	-	-
HM	70	148	160	190	1.8	4.1	12	30	40	28	-	-	-	-
NM	100	170	130	190	4.9	9.8	5	15	72	67	4.07	6.27	1.87	3.46
HM	78	175	150	260	3.0	6.2	11	20	57	36	1.54	3.06	0.91	-
		(160)		(250)		(5.9)		(25)		(36)		(1.98)		
JN	65	180	130	170	2.4	7.3	15	48	63	67	1.79	4.49	1.48	2.58
*PN	78	144	150	210	3.5	10.2	12	17	63	51	2.31	3.02	1.31	1.33
GN	65	170	140	210	3.2	11.6	8	15	67	58	1.45	6.01	0.94	2.94
NP	80	150	130	160	3.1	8.4	10	37	49	46	1.54	4.07	0.92	1.62
MvB	80	120	160	210	2.5	4.0	15	35	51	49	2.33	2.88	1.0	1.63
Mean	84	150	154	212	3.0	6.7	17	30	54	45	2.17	3.31	1.12	1.59
±SD	14	20	17	37	0.7	2.3	9	11	13	15	0.85	1.41	0.42	0.81
(EWL)		149		211		6.6		30		45		3.27		1.60
		20		35		2.3		11		15		1.44		0.81

VII.4.3.2 POSTOP SUPINE:

These results, including the equivalent workload data, are summarised in table 7.34 overleaf.

Heart Rate

The group mean heart rate at rest and on peak exercise was unchanged. Fewer patients (2 as opposed to 5) had a resting tachycardia at the time of the postoperative study.

Systolic Blood Pressure

The mean resting systolic blood pressure was slightly lower at 138 ± 23mmHg, p = NS. Three patients showed an increase in systolic blood pressure (157 ± 12 to 180 ± 13mmHg). At peak exercise systolic blood pressure rose appropriately (mean 189 ± 27mmHg), but was significantly lower than pre-operatively ($p < 0.05$).

Cardiac Index

The group mean resting cardiac index was similar to the pre-operative value (3.1 ± 0.5 versus 3.0 ± 0.7L/min/M^2), and only 1 patient (compared to 6 patients pre-operatively) had a reduced cardiac index. This patient had a markedly reduced pre-operative value of 1.8L/min/M^2. At peak exercise, there was a significant increase in cardiac index to 7.0 ± 1.5L/min/M^2 ($p < 0.01$), which was similar to the pre-operative value of 6.7 ± 2.3L/min/M^2.

Pulmonary Capillary Wedge Pressure(PCWP)

The mean postoperative resting PCWP was normal at 14 ± 4mmHg. However, 6 patients(32%) had an elevated PCWP at rest, 3 of whom had normal pre-operative values. Only one of this subset of patients had a reduced resting cardiac index.

Table 7.34: POSTOPERATIVE RESTING AND PEAK EXERCISE HAEMODYNAMIC AND ERNA DATA: (SUPINE ISOTONIC) (n = 19)

	HR		SBP		CI		PCWP		LVEF		PFR		ADFR	
	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex
FA	74	145	140	210	2.6	7.2	10	15	65	66	2.25	5.06	1.01	1.49
RC	65	155	110	170	2.9	5.0	12	35	25	14	0.85	0.97	0.43	0.50
		(100)		(150)		(4.8)		(25)		(25)		(0.97)		(0.50)
MdV	75	185	120	165	3.2	6.3	13	43	90	85	-	-	-	-
		(120)		(150)		(4.9)		(33)		(89)				
EG	94	138	130	190	4.0	7.7	10	26	72	66	2.70	2.20	1.42	1.12
		(115)		(170)		(6.6)		(20)		(69)		(2.19)		(1.22)
KG	60	150	190	210	2.8	8.4	23	43	70	76	2.75	4.45	1.10	-
		(98)		(180)		(4.6)		(29)		(74)		(4.13)		(1.82)
MH	70	130	140	210	3.2	7.4	18	25	74	70	3.62	6.85	1.20	3.00
BH	82	135	150	200	2.7	4.9	10	12	63	75	1.92	3.80	0.77	1.69
		(110)		(190)				(11)		(68)		(3.36)		(1.59)
JL	78	162	130	180	4.3	9.1	16	25	55	52	2.73	4.68	1.06	1.93
		(142)		(180)		(9.3)		(25)		(54)		(3.43)		(1.34)
NL	88	176	130	155	3.7	7.1	14	20	59	74	1.92	6.60	0.79	3.03
		(150)		(150)		(6.8)		(20)		(66)		(6.13)		(2.09)
ML	120	-	160	-	-	-	-	-	55	-	3.19	-	1.93	-
SM	80	190	120	185	3.0	8.4	13	30	76	81	-	-	-	-
		(150)		(170)		(6.1)		(26)		(79)				
HM	90	168	160	230	2.4	4.4	17	28	41	40	1.96	3.38	0.77	1.80
NM	120	178	120	150	-	-	13	15	76	83	5.59	6.27	2.61	3.80
		(158)		(150)				(13)		(79)		(7.24)		(2.35)
HM	98	160	140	180	3.4	6.0	6	10	58	49	2.69	5.21	1.39	2.72
JN	60	160	110	160	3.0	7.0	14	38	60	77	1.36	5.61	0.40	3.16
PN	78	145	190	225	3.0	8.9	20	38	70	59	2.60	3.33	1.22	1.28
GN	65	174	130	220	3.0	8.9	14	17	64	72	2.65	6.66	1.07	3.16
		(150)		(200)		(8.3)		(15)		(73)		(7.67)		(3.40)
NP	70	150	120	150	2.9	7.7	12	23	65	79	2.01	3.81	0.90	-
		(105)		(130)		(5.6)		(18)		(69)		(3.20)		
MvB	90	120	135	220	2.9	5.0	19	30	55	64	3.55	3.92	1.50	2.30
		(114)		(190)		(4.5)		(33)		(61)		(3.76)		(2.10)
Mean	82	157	138	189	3.1	7.0	14	26	63	66	2.61	4.55	1.15	2.21
±SD	17	19	23	27	0.5	1.5	4	10	14	18	1.05	1.66	0.54	0.96
(EWL)		134		179		6.3		23		65		4.47		1.99
		23		28		1.6		9		15		1.88		0.81

At peak exercise, the PCWP rose signifcantly to 26 ± 10mmHg (range 10 to 43mmHg, p <0.01), which was similar to the pre-operative value of 30 ± 11mmHg. Although only 4 patients(20%) had a normal postoperative peak supine exercise PCWP, this is twice the pre-operative number.

Left Ventricular Ejection Fraction(LVEF)

There was a slight improvement in mean resting supine LVEF to 63 ±

14% compared with 54 ± 13% pre-operatively, p = NS. However, only 2 patients(10%) had an abnormal resting value of < 50% which is markedly improved from the pre-operative number of 8 patients, or 42% of cases.

Seven patients (37%) had a pre-operative resting LVEF < 45% with 3 patients having values of < 40% (N.L. 33%, M.L. 34%, H.M. 40%). Two of the three patients in this subset and 3 out of 4 in the range 40 to 45% normalised their postoperative resting LVEF. Thus it would appear that an abnormal resting LVEF is reversible in the majority of patients undergoing successful aortic valve replacement despite the degree of pre-operative depression. However, very few patients had a markedly reduced resting LVEF < 35% (n = 2) and the surgical outcome in this subset remains to be answered.

At peak exercise there was a marginal increase in LVEF to 66 ± 18%. However, this value was significantly higher than the pre-operative value of 45 ± 15%, p < 0.01. Nine patients (47%) had a pre-operative peak exercise LVEF < 40% and included all the patients (n = 7) with a resting LVEF < 45%. In this subset 7 of 9 patients (78%) normalised their postoperative resting LVEF and 5 of 8 (63%) had an exercise LVEF > 50%. Thus, although a significantly depressed pre-operative exercise LVEF is usually associated with an appreciable reduction in resting ejection fraction, it does not appear to be a poor prognostic marker in the assessment of patients with chronic severe AR.

Peak Filling Rate(PFR)

The resting value increased, albeit non-significantly, to 2.61 ± 1.05 EDV/sec from the pre-operative value of 2.17 ± 0.85 EDV/sec. There was a significant increase at peak exercise to 4.55 ± 1.66

EDV/sec (p <0.01), which is a marked improvement from the pre-operative value of 3.31 ± 1.41 EDV/sec. This implies a substantial improvement in diastolic function postoperatively, as exercise heart rates were similar.

Average Diastolic Filling Rate(ADFR)

Although the resting postoperative and pre-operative mean values were similar (1.15 ± 0.54 EDV/sec versus 1.12 ± 0.42 EDV/sec), the peak exercise value of 2.21 ± 0.96 EDV/sec was significantly improved from the pre-operative value of 1.59 ± 0.81 EDV/sec (p <0.01), confirming the improvement in LV relaxation.

Exercise Capacity

The external workload achieved postoperatively for the group improved appreciably from 400 ± 185 to 514 ± 155k-pm/min (p <0.05)with a range of 250 to 900k-pm/min. This represents approximately 3.5 levels or 10.5 minutes of exercise and a 40% improvement on pre-operative exercise duration.

VII.4.3.3 PRE- AND POSTOPERATIVE SUPINE EWL:

Most of the reported studies in patients with chronic aortic regurgitation compare peak exercise variables pre- and postoperatively, often at different external workloads. This results from a generally improved exercise capacity in the postoperative period. As my data was acquired for each level of graded supine, symptom-limited bicycle exercise, I am able to compare both haemodynamic and ERNA data at equivalent workloads(EWL), with the bracketed numbers in the tables representing those values. In general, this was one or two levels below postoperative peak supine exercise, although in two cases

pre-operative exercise capacity was better than that achieved postoperatively.

Heart Rate/Systolic Blood Pressure

In the postoperative period at equivalent external workloads, the mean heart rate was lower (134 ± 23 vs 149 ± 20/min, $p < 0.05$) as was systolic blood pressure (179 ± 28 vs 211 ± 35mmHg, $p < 0.01$). Thus at the same external workload, the rate-pressure product or internal workload was also lower (23986 vs 31439).

Cardiac Index

Cardiac index, however, was similar at 6.3 ± 1.6L/min/m^2 and did not differ appreciably from the peak supine exercise values noted above.

Pulmonary Capillary Wedge Pressure(PCWP)

When corrected for equivalent external workload, there was a slight decrease in PCWP to 23 ± 9mmHg compared to 26 ± 10mmHg at peak exercise. However, in 3 of 12 patients(25%), the PCWP at equivalent external workload was appreciably lower than that at peak PCWP (25 vs 35mmHg; 33 vs 43mmHg; 29 vs 43mmHg). Nevertheless, this resulted in only one further patient (i.e. a total of 5 patients) having a normal exercise PCWP.

Left Ventricular Ejection Fraction(LVEF)

The pre- and postoperative supine exercise LVEF values at equivalent workloads were identical to that at peak exercise (45 ± 15 and 45 ± 15 and 65 ± 15 and 66 ± 18%).

Peak Filling Rate/Average Diastolic Filling Rate

Once again, the values at peak exercise and those at equivalent external workloads did not differ significantly:-

PFR (3.31 ± 1.41 to 4.55 ± 1.66 versus 3.27 ± 1.44 to 4.47 ± 1.88 EDV/sec.)

ADFR (1.59 ± 0.81 to 2.21 ± 0.96 versus 1.60 ± 0.81 to 1.99 ± 0.81 EDV/sec.)

In summary, a comparison of pre- and postoperative supine exercise haemodynamic and ERNA data at equivalent external workloads, show litte change from values at peak supine exercise but confirms that at equivalent external workloads, the rate-pressure product is considerably reduced postoperatively.

VII.4.3.4 PRE-OP ERECT:

The pre-operative erect resting and peak exercise haemodynamic and radionuclide data is summarised in Table 7.35 overleaf. The resting and peak exercise haemodynamics are similar to those for the symptomatic group as a whole although peak exercise cardiac index was lower(5.7 ± 2.7 versus 6.8 ± 1.8 L/min/M^2). In contrast both resting and peak exercise radionuclide determined LVEF, PFR and ADFR were lower in the subgroup undergoing aortic valve replacement when compared to the overall group (see sections VII.2.2.2A and VII.2.2.2B). The pre-operative data is summarised as follows:-

1. The difference at rest compared to the supine posture can be explained by the predictable haemodynamic changes related to posture.
2. Left ventricular ejection fraction was similar in the two postures and a reduced resting LVEF was present in both body positions in the same patient.
3. The haemodyanmic response was directionally similar to that during supine exercise with the same magnitude of change in

cardiac index, but a lower SBP and a slightly lower exercise PCWP (22 ± 7 versus 30 ± 11mmHg).

4. Similar to the supine posture, most symptomatic patients had an abnormal LVEF response to erect bicycle exercise. Importantly, in the majority of cases the fall in LVEF on exercise occurred during both postures.
5. Diastolic filling rates were reduced nd similar to those obtained during supine exercise.

Table 7.35: PRE-OPERATIVE RESTING AND PEAK EXERCISE HAEMODYNAMIC AND ERNA DATA: (Erect Isotonic) (n = 10)

	HR		SBP		CI		PCWP		LVEF		PFR		ADFR	
	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex
FA	82	160	170	260	2.1	8.0	15	30	56	61	2.99	5.09	1.62	1.58
RC	78	115	160	190	2.3	3.8	5	13	60	45	1.82	1.46	1.03	0.92
EG	110	142	150	200	2.4	5.4	4	12	44	32	2.35	2.12	0.87	0.93
MH	84	160	160	260	1.9	7.0	-	-	41	25	1.86	1.39	0.87	0.67
JL	90	140	135	190	4.0	8.7	9	20	43	30	1.95	2.62	1.25	1.14
NL	120	165	150	180	2.8	5.5	10	18	40	39	1.76	2.69	0.97	0.89
ML	98	160	135	220	2.0	4.6	30	30	36	26	1.66	2.20	0.99	1.07
SM	92	175	150	220	2.4	6.1	7	26	76	69	-	-	-	-
HM	110	190	150	270	2.9	5.8	7	21	59	35	2.41	-	1.39	-
JN	94	170	130	150	2.7	6.2	5	28	61	68	2.49	4.25	1.48	2.70
Mean	96	158	147	214	2.6	5.7	10	22	52	43	2.14	2.73	1.16	1.26
±SD	14	21	11	39	0.6	2.7	8	7	13	17	0.44	1.31	0.28	0.71

VII.4.3.5 POSTOP ERECT:

The postoperative erect resting and peak exercise haemodynamic and radionuclide data is summarised in Table 7.36 overleaf.

Heart Rate

The group had a resting tachycardia of 101 ± 16/min with a range of 72 to 120/min. This was slightly higher than the pre-operative rate of 96 ± 14/min. At peak exercise the heart rate increased to 161 ± 18/min which was similar to that achieved in the pre-operative study (158 ± 18/min). In comparison to the postoperative supine study, the resting heart rate was significantly higher (101

versus 82/min), but the heart rate achieved at peak exercise (equivalent external workloads) was similar (161/min versus 157/min).

Table 7.36 POSTOPERATIVE RESTING AND PEAK EXERCISE HAEMODYNAMIC AND ERNA DATA: (Erect Isotonic) (n = 18)

	HR		SBP		CI		PCWP		LVEF		PFR		ADFR	
	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex
FA	90	155	140	200	2.6	6.9	10	14	64	65	2.38	3.15	1.20	1.31
RC	84	170	125	160	2.9	4.9	6	28	22	14	-	-	-	-
MdV	116	186	130	150	2.7	5.9	8	35	87	90	-	-	-	-
EG	108	135	130	170	3.9	8.2	9	14	81	79	2.35	4.48	1.26	2.36
KG	72	148	160	190	2.3	9.3	10	38	85	90	3.01	4.98	1.13	2.32
MH	86	130	160	200	2.7	8.3	10	23	75	76	4.59	8.05	2.29	3.28
BH	95	150	135	190	2.1	5.5	3	6	72	73	2.60	-	1.04	-
JL	112	162	130	170	3.7	10.0	8	19	53	58	2.51	4.71	1.08	1.49
NL	118	172	130	160	3.9	8.0	6	15	69	84	3.63	3.63	1.31	2.96
SM	118	190	130	185	3.1	8.3	7	30	85	91	-	-	-	-
HM	100	165	150	220	2.0	3.6	10	25	44	44	2.28	2.57	0.92	1.15
NM	130	180	110	150	-	-	3	8	91	87	5.71	-	2.15	-
HM	120	170	130	180	2.9	6.4	7	10	81	67	3.49	3.55	1.70	-
JN	88	170	105	155	2.8	6.4	10	27	77	94	2.67	7.91	1.29	2.70
PN	85	160	180	205	2.8	11.1	5	20	72	64	2.74	2.90	1.40	1.29
GN	94	170	125	185	2.9	9.9	5	14	69	73	3.62	6.13	1.55	2.33
NP	100	150	110	140	3.4	7.6	9	13	73	67	3.23	2.86	1.49	1.70
MvB	105	132	130	200	2.3	5.2	11	25	71	66	3.51	5.53	1.82	3.04
Mean	101	161	134	178	2.9	7.4	8	20	71	71	3.22	4.65	1.46	2.16
±SD	16	18	11	23	0.6	2.0	3	9	17	19	0.94	1.83	0.41	0.75

Systolic Blood Pressure

The mean resting SBP fell marginally by 13mmHg from 147 ± 11mmHg pre-operatively to 134 ± 19mmHg at 6 months postoperatively (p = NS). This value was similar to the resting supine postoperative value of 138 ± 23mmHg. There was a significant increase in SBP at peak exercise to 178 ± 23mmHg ($p < 0.01$) which was appreciably lower than the pre-operation mean of 214 ± 39mmHg ($p < 0.01$). Because of the higher resting heart rate, the rate-pressure product (RPP) at rest in the erect posture was higher than in the supine posture (13534 vs 11316), but at peak exercise the values were similar (28658 vs 29673).

Cardiac Index

Cardiac index rose from a resting level of 2.9 ± 0.6L/min/M^2 to 7.4 ± 2.0L/min/M^2 ($p < 0.01$) at peak exercise. Only 4 patients (24%) had a reduced postoperative resting cardiac index of < 2.5L/min/M^2 compared to 60% of the patients pre-operatively. However, the mean values at rest were similar at 2.9 ± 0.6 vs 2.6 ± 0.6L/min/M^2. In contrast, the cardiac index at peak exercise was appreciably higher (7.4 ± 2.0 versus 5.7 ± 2.7L/min/M^2, $p < 0.01$) but at a higher external workload (514 ± 155 vs 400 ± 185k-pm/min). These results are similar to those recorded during supine exercise.

Pulmonary Capillary Wedge Pressure(PCWP)

All patients had a normal postoperative erect resting PCWP with a mean of 8 ± 3mmHg. At peak exercise, this increased to 20 ± 9mmHg but 44% of patients had a normal exercise PCWP, which is twice the pre-operative number. Nevertheless, the pre- and postoperative mean values at rest (10 ± 8 and 8 ± 3mmHg) and peak exercise (22 ± 7 and 20 ± 9mmHg) were similar. This is in contradistinction to the postoperative supine PCWP where despite the mean resting value decreasing from 17 ± 9 to 14 ± 4mmHg, one third of patients had an abnormal PCWP at rest. In addition, the peak exercise PCWP was higher at 26 ± 10mmHg(compared to 20 ± 9mmHg), with only 22% (i.e. half the erect number) having a normal peak exercise PCWP. Thus, although in the erect posture the mean pre- and postoperative PCWP remained essentially unchanged, all patients normalised their resting PCWP postoperatively and twice the pre-operative number normalised their peak exercise PCWP. In contrast, during supine exercise, one third (33%) still had an abnormal postoperative resting PCWP, with only 22% having a normal peak exercise value (half the number during the erect posture).

Left Ventricular Ejection Fraction(LVEF)

The resting postoperative LVEF in the erect posture improved markedly from 52 ± 13 to 71 ±17% ($p < 0.01$) with a range of 22 to 91%. Only 2 patients(11%) had an LVEF < 50% compared to half the patients pre-operatively. This value is also higher than the postoperative mean of 63 ± 14% during supine exercise.

The LVEF remained unchanged at peak exercise (71 ± 19%, range 14 to 94%) which is slightly higher than during supine exercise (66 ± 18%). Only 2 patients had an abnormally low exercise LVEF, both these patients having an abnormal resting value. This is in marked contrast to the pre-operative period where the majority (70%) had a significantly reduced peak exercise LVEF (mean 33 ± 7%, range 25 to 45%). One third of this group (6 patients) had a normal functional reserve, with 7 patients having an equivocal response (LVEF remained unchanged) and only 5 patients having an abnormal response. Interestingly, 4 of the 5 patients with an abnormal response and 5 of the 7 patients with an equivocal response had a resting postoperative LVEF of > 70% (74 ± 5% and 81 ± 8%). It has been suggested that in patients with a resting LVEF > 70% there may be no further increase in LVEF on exercise.

Peak Filling Rate(PFR)

In the postoperative evaluation, the erect rest PFR increased significantly from 2.14 ± 0.44 to 3.22 ± 0.94 EDV/sec ($p < 0.05$), representing a 50% improvement. At peak exercise there was an even greater 70% improvement from the pre-operative value of 2.73 ± 1.31 to 4.65 ± 1.83 EDV/sec ($p < 0.01$), implying a substantial improvement in both resting and exercise diastolic function. Although the supine resting value postoperatively was appreciably

lower, the peak exercise value is similar (4.55 ± 1.66 vs 4.65 ± 1.83 EDV/sec).

Average Diastolic Filling Rate(ADFR)

Similarly, there was an improvement in both the resting and peak exercise average diastolic filling rates from a pre-operative resting mean of 1.16 ± 0.28 to 1.45 ± 0.41 EDV/sec (26% improvement, p = NS) and a more marked 71% peak exercise improvement from 1.26 ± 0,71 to 2.16 ± 0.75 EDV/sec (p <0.01). Although the resting supine postoperative mean of 1.15 ± 0.54 EDV/sec was substantially lower than the rest erect value (vide supra), the peak exercise results were also similar (2.21 ± 0.96 vs 2.16 ± 0.75 EDV/sec.).

Exercise Capacity

The improvement in external workload achieved postoperatively is the same as during supine exercise (vide supra).

VII.4.3.6 SUPINE ISOMETRIC

The isometric handgrip exercise data will compare the haemodynamic, ejection fraction and diastolic filling rate responses pre- and postoperatively and is summarised in Table 7.37. The workload achieved during each evaluation was essentially unchanged (28 ± 5 and 29 ± 5 lb).

Heart Rate

There was a slight diminution in exercise heart rate between the pre- and postoperative studies (90 ± 16 to 81 ± 12/min, p = NS). Although there was a slight increase in exercise heart rate from rest in the pre-operative study (84 ± 14 to 90 ± 16/min), the

LVEF response to isometric exercise from a mean pre-operative value of 52 ± 14% to 63 ± 15% postoperatively, this occurred parri passu with the improved resting LVEF (54 ± 13 to 63 ± 14%). In the overwhelming majority(93%) of pre-operative studies, the LVEF remained unchanged from the resting value. In the postoperative period the majority 72% also remained unchanged with 2 patients(11%) having a normal functional reserve and 3 patients (17%) a fall in exercise LVEF.

Table 7.37: PRE- AND POSTOPERATIVE HAEMODYNAMIC AND ERNA DATA: (Supine Isometric) (n = 14; n = 18)

	HR		SBP		CI		PCWP		LVEF		PFR		ADFR	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
FA	80	80	210	170	2.9	2.4	28	11	60	53	3.13	1.87	1.51	0.88
RC	70	70	180	130	2.6	3.0	20	13	46	20	1.12	0.87	0.45	0.24
MdV	82	70	190	130	3.7	2.8	24	14	70	90	2.43	-	1.52	-
EG	98	94	170	145	2.5	3.8	15	12	43	71	1.99	2.65	1.02	1.51
KG	100	64	180	200	1.9	3.0	25	23	59	71	3.36	2.88	1.87	0.93
MH	80	70	190	155	2.6	2.9	-	18	45	71	2.38	3.18	0.78	1.22
BH	-	78	-	160	-	2.8	-	12	-	64	-	1.97	-	1.10
JL	85	77	140	150	3.8	4.9	29	17	40	53	2.61	2.56	1.22	0.94
NL	120	96	155	140	3.8	3.9	18	16	34	61	1.07	2.81	0.57	1.05
ML	110	-	160	-	1.6	-	50	-	30	-	2.12	-	0.95	-
SM	96	80	180	130	3.4	3.0	21	12	72	83	-	-	-	-
HM	-	88	-	180	-	3.6	-	18	-	46	-	1.57	-	0.75
NM	110	110	145	125	5.5	-	6	10	72	77	-	4.90	2.01	2.37
HM	84	95	170	140	3.3	3.4	13	8	54	59	-	2.39	1.03	1.38
JN	65	65	130	115	2.6	3.1	16	15	62	57	1.58	1.27	-	0.84
PN	-	75	-	210	-	3.0	-	24	-	68	-	2.50	-	1.26
GN	-	72	-	135	-	3.1	-	14	-	59	-	2.45	-	0.90
NP	-	75	-	125	-	3.3	-	14	-	68	-	-	-	0.94
MvB	85	90	165	150	2.5	2.9	15	23	43	55	1.99	3.81	1.01	1.55
Mean	90	81	169	149	3.1	3.2	22	15	52	63	2.16	2.51	1.16	1.11
±SD	16	12	22	26	1.0	0.6	11	5	14	15	0.73	1.58	0.48	0.46

Peak Filling Rate/Average Diastolic Filling Rate

Although a small (16%) but insignificant increase occurred in PFR during handgrip exercise from 2.16 ± 0.73 pre-operatively to 2.51 ± 1.58EDV/sec postoperatively, the ADFR remained essentially unchanged (1.16 ± 0.48 and 1.11 ± 0.46 EDV/sec).

VII 4.4 SUMMARY OF SIX MONTH POSTOP DATA

1. Excellent symptomatic relief was noted following aortic valve replacement, with most patients in NYHA class I.
2. Regression of LVH was complete (CSA $< 20cm^2$) or near-complete (CSA $< 24cm^2$) in the majority of patients (12/18). By discriminant analysis, regression of LVH could be accurately predicted by the following non-invasive variables:-
   (i) DED < 7.0cm
   (ii) CSA $< 30cm^2$
   (iii) Resting LVEF > 50%
   (iv) Maximum exercise HR > 148/min.
   (v) Exercise SBP > 220mmHg
3. There was a progressive reduction in DED over the 6 month period, although a pre-operative value of > 8.0cm was associated with persistent LV dilatation. By contrast, albeit a small sample size (n = 5), a pre-operative DES > 5.5cm was not associated with a poor postoperative result.
4. Resting haemodynamics remained unchanged. During supine bicycle exercise, SBP was significantly lower but exercise PCWP remained markedly elevated (26 $\pm$ 10mmHg versus 30 $\pm$ 11mmHg pre-op) - only 1/5 of patients had a normal postoperative exercise PCWP.
5. An abnormal resting LVEF pre-operatively was reversible in the majority of patients undergoing successful AVR - however, very few patients had a marked reduction in LVEF <35% and the surgical outcome in this subset remains unanswered. Similarly, a significantly reduced pre-operative exercise LVEF (<40%) was not a poor prognostic marker. This improvement in systolic function was parallelled by improved LV relaxation both at rest

and on exercise.

6. Similar changes in haemodynamics and radionuclide variables were noted during erect bicycle exercise.

VII.5.0 SEQUENTIAL STUDIES

Sequential studies at 6 monthly intervals were performed in a total of 26 patients, 23 asymptomatic subjects and 3 patients with early symptoms who refused valve replacement surgery. Nine of these patients (including one of the symptomatic group) were subsequently re-evaluated at 12 months after their initial assessment. Although this latter cohort of patients is significantly smaller than the one assessed at 6 months, the results from this part of the study will be included as they provide both completeness and some important and interesting observations, particularly with regard to the progression of the haemodynamic burden and its effects on LV function.

Two asymptomatic patients developed symptoms at 12 to 18 months after their initial assessment and underwent successful aortic valve replacement. The one patient (A.C.) developed dyspnoea on effort associated with progressive LV dilatation, a rise in both resting and peak exercise pulmonary capillary wedge pressure but an unchanged resting LVEF. At 6 months postoperatively he was asymptomatic, had near-normalised his LV size (DED 5.5cm, DES 4.6cm) but had marginally abnormal resting LVEF of 45% (pre-operative LVEF 55%). The second patient (J.J.) underwent aortic valve replacement for recurrent severe chest pain requiring hospitalisation. At cardiac catheterisation 12 months earlier he had normal coronary arteries. Although he had a slight increase in LV size at sequential evaluation, both resting and exercise

haemodynamics and radionuclide measures remained unchanged and six months postoperatively he was asymptomatic with normal echocardiographic dimensions and resting LV contractile function.

Each study included an assessment of clinical status, echocardiographic LV dimensions and systolic function and an exercise evaluation including haemodynamic monitoring and simultaneous equilibrium radionuclide angiocardiography as outlined previously. Repeat cardiac catheterisation was not performed.

VII.5.1 CLINICAL STATUS

VII.5.1.1 Functional Class

None of the 23 asymptomatic patients developed any symptoms over the 6 to 12 month follow up period and all 3 symptomatic patients remained in functional class II(NYHA).

VII.5.1.2 Left Ventricular Hypertrophy on Electrocardiogram

All patients had severe left ventricular hypertrophy with repolarisation change as assessed by the Sokolow Lyon index, with 6 patients having a pseudo-anterior myocardial infarct pattern. Over the 6 to 12 months follow up period no significant change occurred.

VII.5.1.3 Cardio-Thoracic Ratio(CTR)

The mean CTR at initial assessment was 0.56 $\pm$ 0.06 (range 0.48 to 0.69) and remained essentially unchanged at 6 and 12 month assessments. Five patients had an increase of > 0.04 in CTR (range 0.04 to 0.09), but in only one of these(PJ) was there a simultaneous increase in echocardiographic LV DED from 6.6 to 7.0cm.

VII.5.2 ECHOCARDIOGRAPHY

Table 7.38 summarises the serial echocardiographic LV dimensions and systolic function for the 26 patients over the 6 to 12 month follow up period.

Table 7.38: SERIAL EVALUATION OF ECHOCARDIOGRAPHIC DATA:

	DED			DES			%FS			WS		
	0	6	12	0	6	12	0	6	12	0	6	12
*SA	6.3	6.1	-	4.2	4.2	-	33	31	-	473	441	-
LA	7.1	7.1	-	4.8	4.4	-	32	38	-	473	524	-
SA	7.6	6.5	7.4	5.2	4.5	5.5	32	31	26	950	406	592
*MB	6.7	6.3	-	4.2	4.3	-	36	31	-	670	339	-
*AC	7.6	8.5	8.0	5.0	5.8	5.8	34	32	26	409	580	680
DD	7.3	7.3	-	4.8	5.0	-	34	32	-	477	564	-
HH	7.5	7.2	7.3	5.5	5.2	5.8	27	31	21	433	425	378
PJ	6.6	7.0	-	4.4	4.8	-	33	31	-	420	544	-
*JJ	6.6	7.2	-	4.8	4.8	-	27	33	-	396	540	-
KK	7.2	7.0	8.5	5.0	4.4	4.9	30	37	42	491	400	638
*GM	5.9	6.2	-	3.9	4.0	-	34	35	-	369	496	-
PM	-	7.6	7.3	-	4.7	5.0	-	38	32	-	760	840
*NO	6.8	7.1	6.8	4.1	4.1	4.7	40	42	31	418	410	482
MP	6.0	6.3	-	4.4	4.7	-	26	25	-	369	441	-
SR	6.0	6.0	-	3.8	3.4	-	37	40	-	375	280	-
WS	5.0	6.3	-	3.0	4.0	-	40	36	-	341	490	-
TS	7.9	7.3	-	4.8	5.0	-	39	31	-	490	449	-
FT	7.2	6.3	-	5.0	5.1	-	30	19	-	420	341	-
VdS	8.2	7.0	6.8	5.4	4.6	4.5	34	34	34	547	630	419
LV	7.9	8.2	78	5.3	5.5	5.2	34	33	33	600	581	390
*CV	5.5	5.9	-	3.5	3.7	-	36	37	-	330	285	-
*DV	6.1	5.9	-	4.1	4.1	-	33	30	-	305	375	-
*AW	5.2	5.4	-	3.6	3.3	-	31	39	-	416	315	-
MA	7.2	6.3	7.2	4.8	3.9	4.2	33	38	42	589	334	524
DD	5.3	5.1	-	3.4	3.2	-	36	37	-	331	325	-
MN	7.1	7.3	-	4.6	4.5	-	35	38	-	443	477	-
MEAN	6.7	6.7	7.5	4.5	4.4	5.1	33	34	32	461	452	549
±SD	0.9	0.8	0.6	0.7	0.6	0.6	4	5	7	135	117	153

* GROUP 2A

0 = Initial assessment
6 = Six month assessment
12 = Twelve month assessment

VII.5.2.1 LV Dimensions

The mean LV DED remained unchanged at the 6 month follow up assessment (6.7 ± 0.8 vs 6.7 ±0.9cm). Three patients (12%) had a significant increase in LV DED at 6 month evaluation (mean 6.4 ±

1.3 to 7.3 ± 1.1cm). Importantly, in 4 patients a decrease in dimension from 7.7 ± 0.4 to 6.8 ± 0.5cm was recorded. Only one patient (KK) increased his LV DED at the 12 month assessment from 7.2 to 8.5cm and it remained at 8.0cm at the 18 month assessment. The LV DES also remained unchanged (4.4 ± 0.6 vs 4.5 ± 0.7cm at initial assessment) with a range of 3.0 to 5.5cm. Only 1 patient (AC) had a significant increase in LV DES from 5.0 to 5.8cm at 6 months, remaining at this value at the 12 month assessment. Six months later (i.e. 18 months after the initial assessment), this patient developed symptoms and underwent successful aortic valve replacement. One patient (HH) had an initial LV DES of 5.5cm, with a measurement of 5.2cm at 6 months and 5.8cm at 12 months, but to date remains asymptomatic and well.

VII.5.2.2 LV Systolic Function

As occurred with the LV dimensions, fractional shortening(%FS) 4 remained unchanged over the 6 to 12 month reassessment period. mean %FS at initial assessment was 33 ± 4% with a range of 26 to 40%. Three patients had a moderate increase in %FS over the first 6 month period (29 ± 2 to 36 ± 3%) with one of these (KK) having a further increase in %FS from 37 to 42% at the 12 month assessment. This same patient increased his LV DED from 7.2 to 8.5cm over this period.

Two patients significantly decreased their %FS (TS 39 to 31%; FT 30 to 19%) over the 6 month period but with no change in resting LVEF assessed by equilibrium radionuclide angiocardiography (vide infra).

VII.5.2.3 LV Systolic Wall Stress(WS)

In all but 2 patients the WS was normal at initial assessment with

a mean of 461 ± 135mmHg and a range of 305 to 950mmHg. It remained essentially unchanged at the 6 month evaluation with a mean of 452 ± 117mmHg. However, in 10 patients (38%) there was an appreciable increase in WS of > 50mm from a mean of 411 ± 72 to 518 ± 73mmHg. In only 3 of these patients was there a significant increase in LV DED to explain this increased stress. In both patients with abnormal initial values (SA; LV) there was a decrease in WS, in one primarily due to reduction in LV dimension and the second due to an increase in LV posterior wall thickness (increased LV hypertrophy).

At the 12 month assessment, there was a slight increase in WS in 6 of the 9 patients studied with the mean value increasing from 503 ± 140 to 549 ± 153mmHg.

VII.5.3 EXERCISE EVALUATION

The serial exercise evaluation included resting and peak exercise haemodynamic and equilibrium radionuclide angiocardiographic(ERNA) data in both the supine and semi-erect postures. Patients were once again stratified according to their exercise LV functional reserve at initial assessment. Those with an equivocal or normal response constituted group 2A(n=9) and those with a > 5% drop in exercise LVEF group 2B(n=17).

VII.5.3.1 Serial Supine Resting Haemodynamics

In the group as a whole, there was no appreciable change in heart rate and SBP but a significant decrease in resting cardiac index at 12 months in the 9 patients studied at that time ($p < 0.01$). There was a progressive increase in PCWP from 16 ± 4 to 18 ± 4 and 20 ± 4mmHg over the 12 month period ($p < 0.01$). This data is outlined in Table 7.39.

Table 7.39: SERIAL EVALUATION OF SUPINE RESTING HAEMODYNAMICS:

	HR			SBP			CI			W		
	0	6	12	0	6	12	0	6	12	0	6	12
*SA	78	70	-	150	135	-	3.5	2.8	-	13	17	-
LA	70	70	-	165	160	-	2.9	2.9	-	16	19	-
SA	70	72	66	170	160	160	3.0	3.3	2.9	12	18	18
*MB	72	68	-	150	120	-	2.8	3.4	-	21	21	-
*AC	90	90	88	160	150	140	3.1	3.2	2.8	16	20	22
DD	76	78	-	170	170	-	2.9	4.2	-	20	23	-
HH	70	66	70	160	140	140	3.4	2.8	2.1	18	23	18
PJ	90	88	-	140	130	-	4.4	3.9	-	14	13	-
*JJ	74	72	-	180	170	-	3.8	3.5	-	21	17	-
KK	100	78	80	160	140	150	4.9	3.8	3.8	17	26	25
*GM	70	85	-	150	160	-	2.7	3.8	-	13	15	-
PM	64	64	68	180	200	200	3.5	2.7	2.2	15	18	23
*NO	72	66	68	150	170	180	3.5	3.3	2.9	11	18	15
MP	100	104	-	160	150	-	3.9	3.2	-	15	15	-
SR	78	74	-	160	150	-	2.6	2.3	-	30	26	-
WS	82	76	-	150	160	-	2.8	4.0	-	15	17	-
TS	68	60	-	140	130	-	3.0	2.2	-	20	20	-
FT	84	80	-	140	130	-	4.0	5.2	-	18	15	-
VdS	80	75	70	160	160	160	4.6	4.5	3.1	14	11	15
LV	70	75	70	180	190	160	3.7	4.1	3.6	16	15	18
*CV	66	60	-	120	110	-	3.0	2.5	-	11	15	-
*DV	62	60	-	140	140	-	2.8	3.3	-	16	20	-
*AW	135	120	-	140	140	-	3.4	4.0	-	11	12	-
MA	75	76	64	165	180	160	2.5	2.0	2.1	16	27	23
DD	68	64	-	160	150	-	3.5	3.1	-	20	16	-
MN	70	76	-	155	170	-	3.5	3.4	-	16	20	-
MEAN	78	76	72	156	153	161	3.4	3.4	2.8	16	18	20
±SD	15	14	8	14	12	19	0.6	0.7	0.6	4	4	4

* Group 2A

Table 7.40 SUBSET SERIAL SUPINE RESTING HAEMODYNAMIC DATA: (mean ±S.D.)

	HR			SBP			CI			PCWP		
	0	6	12	0	6	12	0	6	12	0	6	12
2A	80	77	78	149	144	160	3.2	3.3	2.9	15	17	19
	22	19	14	16	21	28	0.4	0.5	0.1	4	3	5
2B	77	75	70	160	157	161	3.5	3.4	2.8	17	19	20
	11	10	5	12	21	19	0.7	0.9	0.7	4	5	4

Similar to the initial assessment in both the symptomatic and asymptomatic groups, heart rate and cardiac index were similar in the two subsets with a higher SBP in group 2B ($p < 0.05$) and thus a higher resting rate-pressure product (12320 vs 11920). Resting

PCWP was similarly normal in group 2A patients (15 ± 4mmHg) and slightly elevated in group 2B.

Heart rate and SBP remained essentially unchanged in both subgroups over the 12 month period - the apparent elevation in SBP at 12 months in group 2A is due to the small sample size of 2 patients with the mean for these two patients at 6 months being 160 ± 14mmHg. Both subsets showed an unchanged resting cardiac index at 6 month assessment but a significant drop occurred at 12 months in group 2B ($p < 0.01$). All Group 2A patients had a normal index of > 2.5L/min/m^2, with 3 of the Group 2B patients(43%) having a progressive fall to an abnormal resting cardiac index at 12 months. Although resting PCWP was normal in group 2A patients (15 ± 4mmHg), 44% had an abnormal value at initial assessment. Six patients had a progressive increase in PCWP at 6 months with 66% now having an abnormal resting PCWP. In contrast, 65% of the group 2B patients had an initial elevation of PCWP with 9 patients having a progressive increase at 6 months and 71% of patients having a PCWP > 15mmHg at this assessment.

Only 2 patients had a further increase in resting PCWP at the 12 month assessment. Thus in both groups there is a progressive increase in PCWP (Group 2A $p < 0.01$, Group 2B $p < 0.05$), with a greater percentage of group 2A patients developing an abnormal PCWP with time.

VII.5.3.2 Serial Supine Resting Radionuclide Data

In the overall group (data outlined in Table 7.41 overleaf) the resting LVEF remained unchanged, but there was a progressive fall in both PFR (2.28 ± 0.75 to 2.12 ± 0.49 at 6 months and 1.93 ± 0.57 EDV/sec at 12 months) and ADFR (1.20 ± 0.39 to 1.09 ± 0.26 and 1.06

± 0.25 EDV/sec at 12 months).

Table 7.41: SERIAL EVALUATION OF SUPINE RESTING RADIONUCLIDE DATA:

	EF			PFR			ADFR		
	0	6	12	0	6	12	0	6	12
*SA	65	59	-	2.46	1.98	-	1.11	0.96	-
LA	63	65	-	1.82	1.96	-	1.17	0.99	-
SA	62	61	62	1.89	1.55	1.62	0.91	0.93	0.91
*MB	64	68	-	1.91	1.91	-	1.03	1.03	-
*AC	55	52	54	3.35	2.67	2.69	1.60	1.37	1.35
DD	61	60	-	2.29	2.20	-	1.03	1.20	-
HH	62	64	56	1.72	1.87	1.69	1.01	1.07	0.82
PJ	59	46	-	2.19	2.25	-	1.35	1.02	-
*JJ	71	71	-	2.12	2.30	-	1.16	1.16	-
KK	62	66	72	2.71	2.86	2.59	1.59	1.25	1.47
*GM	72	73	-	2.23	2.50	-	1.27	1.28	-
PM	58	62	54	1.47	1.18	1.13	0.83	0.85	0.76
*NO	65	70	71	2.19	2.59	2.24	1.02	1.01	1.21
MP	69	63	-	2.41	1.98	-	1.67	1.29	-
SR	66	65	-	2.42	2.45	-	1.21	1.15	-
WS	61	65	-	2.26	2.17	-	1.25	1.24	-
TS	53	53	-	1.37	1.26	-	0.83	0.74	-
FT	50	50	-	1.97	1.76	-	1.21	1.04	-
VdS	66	61	70	2.37	2.18	2.29	1.25	0.97	1.02
LV	65	74	68	1.96	2.39	1.89	1.13	1.41	1.18
*CV	63	63	-	1.79	1.75	-	0.86	0.77	-
*DV	63	62	-	2.19	1.94	-	0.77	0.70	-
*AW	73	70	-	5.35	3.36	-	2.73	1.97	-
MA	57	60	53	1.82	1.46	1.20	0.93	0.96	0.83
DD	78	76	-	2.69	2.56	-	1.34	1.05	-
MN	57	58	-	1.97	1.92	-	1.04	1.05	-
MEAN	63	63	62	2.28	2.12	1.93	1.20	1.09	1.06
±SD	6	7	8	0.75	0.49	0.57	0.39	0.26	0.25

* GROUP 2A

Table 7.42: SUBSET SERIAL SUPINE RESTING RADIONUCLIDE DATA (Mean ±S.D.)

	EF			PFR			ADFR		
	0	6	12	0	6	12	0	6	12
2A	66	65	63	2.62	2.33	2.47	1.28	1.14	1.28
	6	7	12	1.12	0.51	0.32	0.59	0.38	0.10
2B	62	62	62	2.08	2.0	1.77	1.16	1.07	0.99
	6	7	8	0.39	0.46	0.54	0.24	0.17	0.24

In both subgroups resting LVEF remained essentially unchanged over the 12 month period, with only 2 of the group 2B patients having a significant fall in resting LVEF at 6 months (LVEF 59 to 46%)

unassociated with any change in resting haemodynamics, but associated with an appreciable fall in ADFR from 1.35 to 1.02 EDV/sec. One other patient in this subset(HH) had a significant drop in LVEF at the 12 month assessment (LVEF 64 to 56%) associated with an appreciable reduction in cardiac index and ADFR and a slight fall in PFR.

Although the measures of diastolic function remained essentially unchanged in the group 2A patients, there was a small but progressive fall in both PFR (2.08 $\pm$ 0.39 to 2.00 $\pm$ 0.46 at 6 months and 1.77 $\pm$ 54 EDV/sec at 12 months) and ADFR (1.16 $\pm$ 0.24 to 0.99 $\pm$ 0.24 EDV/sec at 12 months) in the Group 2B patients.

VII.5.3.3 Serial Supine Exercise Haemodynamics

In the group as a whole (see table 7.43) heart rate and cardiac index remained unchanged but there was a progressive increase in SBP ($p < 0.01$) and peak exercise PCWP (PCWP 23 $\pm$ 5 to 25 $\pm$ 9 at 6 months, p = NS and 30 $\pm$ 11 at 12 months, $p < 0.01$).

Once stratified into subgroups(table 7.44), the pattern remained unchanged in both subsets, with similar heart rates and cardiac indexes but a higher SBP in the group 2B patients at initial and 6 month assessments ($p < 0.01$) and thus a higher rate -pressure product. There was also a significant increase in SBP in the group 2B subset at 12 months ($p < 0.05$). In addition, group 2B patients had a significantly higher PCW pressure at peak exercise ($p < 0.01$). Although 78% of group 2A patients had a normal peak exercise PCWP (< 15mmHg) at initial assessment, only 33% were normal at 6 months. In contrast, only 12% of group 2B patients had an initial normal exercise PCWP, with no patients having a normal value at 6 months.

Table 7.43: SERIAL EVALUATION OF SUPINE EXERCISE HAEMODYNAMICS:

	HR			SBP			CI			PCWP		
	0	6	12	0	6	12	0	6	12	0	6	12
*SA	200	190	-	220	210	-	9.0	8.2	-	12	15	-
LA	190	180	-	240	230	-	11.4	11.4	-	15	25	-
SA	190	196	184	230	240	240	14.3	12.8	11.7	15	20	30
*MB	165	145	-	230	220	-	10.5	10.5	-	30	28	-
*AC	130	165	162	210	230	250	8.3	9.5	7.5	14	25	35
DD	180	180	-	290	280	-	13.0	14.1	-	28	28	-
HH	165	160	180	250	250	280	9.5	9.3	9.0	17	20	15
PJ	172	186	-	200	200	-	11.1	9.6	-	24	31	-
*JJ	190	172	-	220	210	-	11.7	10.4	-	25	23	-
KK	170	178	180	250	270	280	9.6	12.0	11.6	20	45	40
*GM	160	174	-	230	250	-	8.4	9.7	-	15	18	-
PM	150	150	160	230	215	220	9.3	11.0	9.2	20	25	30
*NO	140	148	160	210	290	280	10.1	10.9	12.5	10	13	15
MP	200	200	-	230	220	-	9.3	8.4	-	28	25	-
SR	140	150	-	220	250	-	7.0	8.4	-	30	38	-
WS	190	178	-	240	250	-	5.9	8.3	-	18	25	-
TS	185	165	-	210	210	-	7.4	8.2	-	38	38	-
FT	190	205	-	220	200	-	9.8	12.3	-	35	33	-
VdS	165	164	160	280	300	300	13.4	11.8	12.7	17	17	24
LV	180	180	182	300	290	290	12.6	15.1	11.9	35	28	32
*CV	168	170	-	210	220	-	11.3	11.0	-	15	15	-
*DV	140	132	-	220	230	-	8.9	10.9	-	15	18	-
*AW	198	170	-	210	190	-	6.9	8.3	-	15	17	-
MA	170	165	160	230	260	220	6.2	6.0	5.6	38	47	50
DD	164	148	-	230	230	-	10.1	9.3	-	28	20	-
MN	180	135	-	250	210	-	8.1	6.1	-	28	23	-
MEAN	172	169	170	233	237	262	9.7	10.1	10.2	23	25	30
±SD	20	19	11	25	30	30	2.2	2.2	2.5	5	9	11

* GROUP 2A

Table 7.44: SUBSET SERIAL SUPINE EXERCISE HAEMODYNAMICS (Mean ± S.D.)

	HR			SBP			CI			PCWP		
	0	6	12	0	6	12	0	6	12	0	6	12
2A	166	163	161	218	228	265	9.5	9.9	10.0	17	19	25
	26	18	1	8	29	21	1.6	1.1	3.5	6	4	14
2B	175	172	172	241	241	261	9.9	10.2	10.2	26	29	32
	16	20	13	27	31	34	3.1	2.6	2.5	8	5	11

In both subsets, although exercise LVEF remained unchanged at 6 months, a significant drop occurred at the 12 month assessment with the group 2A LVEF falling from 66 ± 9 to 54 ± 14% ($p < 0.01$) and the group 2B LVEF from 51 ± 10 to 45 ± 7% ($p < 0.05$). Although

this was associated with a progressive but non-significant decrease in PFR (4.2 ± 1.17 to 3.57 ± 0.67 EDV/sec) and ADFR (1.91 ± 0.61 to 1.74 ± 0.29 EDV/sec) in the group 2B patients, these measures of diastolic filling remained unchanged in the group 2A subset.

VII.5.3.4 Serial Supine Exercise Radionuclide Data

The serial data for the group is summarised in Table 7.45. A slight but progressive increase in exercise capacity is noted over the 12 month period. This may relate to a "training effect", although it is more likely due to familiarisation with the exercise apparatus and protocol. Although there is virtually no change in

Table 7.45: SERIAL EVALUATION OF SUPINE EXERCISE RADIONUCLIDE DATA:

	EF			PFR			ADFR			Ex. Cap		
	0	6	12	0	6	12	0	6	12	0	6	12
*SA	65	57	-	3.84	5.18	-	2.31	2.42	-	550	550	-
LA	56	61	-	5.65	3.77	-	1.17	0.99	-	600	750	-
SA	55	52	44	5.64	4.56	-	2.77	2.57	-	900	1050	900
*MB	62	58	-	4.04	-	-	2.40	-	-	750	750	-
*AC	60	52	44	5.19	5.66	4.87	2.51	2.73	1.92	450	600	600
DD	52	56	-	5.92	5.92	-	2.31	2.76	-	1050	1050	-
HH	57	55	44	4.07	3.53	3.61	2.52	1.51	1.62	600	600	750
PJ	52	43	-	4.99	4.56	-	2.32	2.30	-	750	750	-
*JJ	70	76	-	3.99	4.60	-	2.07	1.91	-	900	750	-
KK	57	53	48	5.93	3.66	2.89	2.62	1.89	1.67	600	750	750
*GM	68	68	-	5.48	5.04	-	2.44	2.61	-	750	900	-
PM	52	53	43	3.07	4.23	3.57	1.29	2.27	1.51	600	750	750
*NO	63	68	64	3.44	4.08	5.46	1.90	2.32	2.95	900	900	1050
MP	59	52	-	4.04	4.73	-	1.83	2.24	-	600	600	-
SR	50	54	-	3.68	4.15	-	1.62	1.59	-	450	600	-
WS	52	55	-	4.64	4.99	-	2.20	2.45	-	600	600	-
TS	33	36	-	2.71	2.75	-	0.75	1.18	-	750	750	-
FT	36	25	-	3.38	2.58	-	1.94	1.41	-	750	900	-
VdS	56	43	54	4.53	4.11	4.81	2.69	2.18	2.30	750	1050	1050
LV	41	58	32	4.36	5.07	3.07	1.92	2.68	1.74	600	900	900
*CV	67	67	-	4.84	6.17	-	2.62	2.75	-	900	900	-
*DV	61	66	-	4.12	5.67	-	1.90	2.20	-	900	1050	-
*AW	83	79	-	6.33	5.98	-	3.36	3.04	-	350	350	-
MA	52	50	47	3.00	2.65	3.46	1.54	1.17	1.58	450	600	600
DD	64	67	-	3.93	6.34	-	2.00	2.90	-	600	450	-
MN	36	48	-	1.99	2.15	-	1.04	1.40	-	450	300	-
MEAN	56	56	47	4.34	4.49	3.97	2.08	2.14	1.91	675	738	817
±SD	8	12	9	1.09	1.17	0.95	0.59	0.60	0.49	178	209	170

* GROUP 2A

peak exercise LVEF or diastolic filling rates at the 6 month assessment, a progressive fall in all 3 radionuclide variables is noted at 12 months (LVEF 56 ± 12 to 47 ± 9%, p <0.01; PFR 4.49 ± 1.17 to 3.97 ± 0.95 EFV/sec, p = NS; ADFR 2.14 ± 0.59 to 1.91 ± 0.49EDV/sec, p = NS).

Three of the nine(33%) group 2A patients and 9/17(53%) of the group 2B patients improved their exercise capacity by 1 level (150k-pm/min) with two of the group 2B patients improving by 2 levels. From table 7.46 it is evident that group 2A patients had a significantly higher exercise LVEF, PFR and ADFR than the Group 2B subset (p <0.01), with no patient having a reduced peak exercise LVEF of < 50%(compared to 4 patients or 24% of group 2B).

Table 7.46: SUBSET SERIAL SUPINE EXERCISE RADIONUCLIDE DATA: (Mean ± S.D.)

	EF			PFR			ADFR			Ex. Cap.		
	0	6	12	0	6	12	0	6	12	0	6	12
2A	67	66	54	4.59	5.30	5.17	2.39	2.50	2.44	717	750	825
	7	9	14	0.94	0.71	0.42	0.45	0.36	0.73	215	218	318
2B	51	51	45	4.21	4.10	3.57	1.91	1.97	1.74	653	732	814
	9	10	7	1.17	1.16	0.67	0.61	0.62	0.29	159	211	146

VII.5.3.5 Serial Erect Resting Haemodynamic Data

In the group as a whole (table 7.47), there was no change in resting heart rate, SBP and cardiac index over the 12 month study period. However, there was a small but progressive increase in PCWP (p <0.01). This is similar to the supine posture although cardiac index fell significantly at the 12 month assessment.

When stratified according to initial exercise LVEF response (table 7.48), the two subgroups of patients had similar serial haemodynamics in the erect posture with a higher resting heart

rate, significantly lower PCWP (p <0.01) and similar SBP and cardiac index values to the supine posture. There was no reduction in resting cardiac index at 12 months, and all patients in both subgroups had a normal serial erect resting PCWP (compared to the supine posture with 44% abnormal in group 2A increasing to 66% abnormal at 6 months; 65% abnormal in group 2B, increasing to 71% abnormal at 6 months). As is evident in the above table, there was a progressive increase in resting PCWP in group 2A patients from 5 ± 2mmHg at initial assessment to 8 ± 3mmHg at 6 months (p <0.05) and 10 ± 2mmHg at the 12 month assessment (p = NS). The PCWP in contrast remained unchanged in the group 2B patients.

Table 7.47: SERIAL EVALUATION OF ERECT RESTING HAEMODYNAMIC DATA:

	HR			SBP			CI			PCWP		
	0	6	12	0	6	12	0	6	12	0	6	12
*SA	104	100	-	110	120	-	3.3	3.1	-	5	6	-
LA	120	112	-	160	150	-	4.6	4.1	-	11	10	-
*SA	80	100	92	150	145	150	3.0	4.2	3.1	6	10	10
MB	92	86	-	145	130	-	3.1	2.9	-	6	9	-
AC	-	105	108	-	140	145	-	3.6	3.1	-	10	9
*DD	102	100	-	160	170	-	4.6	4.0	-	10	9	-
HH	85	95	92	150	160	150	3.7	4.2	3.4	6	12	10
*PJ	112	118	-	130	135	-	4.5	3.3	-	6	9	-
*JJ	110	90	-	160	160	-	4.1	3.0	-	6	11	-
*KK	110	105	110	160	160	150	3.6	3.7	3.3	7	13	8
GM	-	115	-	-	160	-	-	3.4	-	-	7	-
PM	-	70	88	-	160	150	-	2.3	3.0	-	6	6
*NO	98	80	98	150	180	160	3.0	2.5	3.8	2	7	11
MP	136	140	-	150	140	-	3.4	3.4	-	5	12	-
SR	90	98	-	140	150	-	3.5	2.8	-	10	13	-
WS	104	90	-	140	150	-	2.6	3.6	-	10	10	-
TS	98	95	-	130	125	-	3.3	2.6	-	8	7	-
FT	115	110	-	150	125	-	4.3	5.4	-	8	8	-
VdS	-	90	88	-	160	150	-	3.1	3.3	-	3	5
LV	-	95	100	-	160	170	-	5.4	4.6	-	9	5
*CV	84	86	-	120	120	-	-	3.4	-	5	7	-
*DV	72	64	-	150	140	-	3.4	2.8	-	3	4	-
*AW	142	132	-	150	140	-	2.8	3.9	-	4	8	-
MA	-	82	78	-	140	140	-	2.1	2.2	-	15	9
DD	90	85	-	150	140	-	2.9	2.9	-	9	7	-
MN	-	88	-	-	160	-	-	2.8	-	-	6	-
MEAN	102	97	95	145	147	152	3.5	3.4	3.3	7	9	8
±SD	18	17	10	14	16	9	0.6	0.8	0.6	3	3	2

* Group 2A

Table 7.48: SUBSET SERIAL ERECT RESTING HAEMODYNAMICS (Mean ± S.D.)

	HR			SBP			CI			PCWP		
	0	6	12	0	6	12	0	6	12	0	6	12
2A	101	98	100	144	147	153	3.6	3.4	3.4	5	8	10
	20	19	9	18	12	6	1.9	0.6	0.4	2	3	2
2B	103	97	92	146	147	151	3.5	3.4	3.3	8	9	7
	17	16	10	9	13	10	0.6	1.0	0.8	2	3	2

VII.5.3.6 Serial Erect Resting Radionuclide Data

Similar to the supine posture, in the group as a whole (Table 7.49), resting LVEF remained essentially unchanged although there was a small but progressive fall in PFR (2.66 ± 0.76 to 2.53 ± 0.62 at 6 months and 2.46 ± 0.89 EDV/sec at 12 months, p = NS) and ADFR (1.50 ± 0.48 to 1.47 ± 0.34 at 6 months and 1.45 ± 0.49 EDV/sec at 12 months, p = NS). Although the resting LVEF was similar in both postures, both PFR (2.66 ± 0.76 versus 2.28 ± 0.75 EDV/sec) and ADFR (1.50 ± 0.48 vs 1.20 ± 0.39 EDV/sec) were higher in the erect posture, almost certainly related to the higher erect resting heart rate.

Although resting LVEF remained unchanged at 6 months in both subsets, 3 group 2A patients (PJ; DV; AW) and 1 group 2B patient (FT) had progressive reductions in resting LVEF, with all 4 however remaining within the normal range. This reduction in LVEF was associated with an appreciable fall in PFR, a lesser fall in ADFR and in 2 patients it was associated with a reduction in cardiac index. In 3 other patients (SA; PM; MA), the fall in resting LVEF only became apparent at the 12 month assessment, and in all it was associated with an appreciable reduction in diastolic filling rates.

In group 2A, PFR fell at 6 months (2.82 ± 0.85 to 2.61 ± 0.66

EDV/sec) and then plateaued, with ADFR remaining essentially unchanged. In group 2B, PFR and ADFR remained essentially unchanged over the 12 month follow up period.

Table 7.49: SERIAL EVALUATION OF ERECT RESTING RADIONUCLIDE DATA:

	EF			PFR			ADFR		
	0	6	12	0	6	12	0	6	12
*SA	54	63	-	2.50	2.22	-	0.90	1.39	-
LA	-	68	-	-	2.68	-	-	1.38	-
*SA	60	59	55	2.66	3.08	2.45	1.41	1.72	1.54
*MB	63	65	-	1.25	1.69	-	0.75	1.05	-
AC	-	63	65	-	4.09	4.12	-	2.20	2.32
*DD	63	64	-	3.14	3.24	-	1.95	1.94	-
HH	69	67	68	1.89	2.13	2.09	1.19	1.39	1.21
*PJ	61	51	-	3.45	1.96	-	1.92	1.17	-
*JJ	72	71	-	3.40	2.80	-	1.76	1.63	-
*KK	60	63	60	2.52	2.62	2.75	1.56	1.77	1.70
GM	-	68	-	-	2.95	-	-	1.90	-
PM	-	66	49	-	1.50	1.00	-	0.87	0.66
*NO	63	75	-	2.87	2.75	-	1.40	1.41	-
MP	71	60	-	3.20	3.01	-	1.92	1.45	-
SR	67	63	-	2.07	2.71	-	1.44	1.46	-
WS	60	70	-	-	2.43	-	-	1.50	-
TS	54	49	-	2.10	1.79	-	1.18	0.95	-
FT	56	48	-	2.40	2.25	-	1.64	1.34	-
VdS	-	61	67	-	2.50	2.75	-	1.52	1.64
LV	-	62	64	-	2.11	2.58	-	1.33	1.42
*CV	65	70	-	2.25	2.28	-	1.26	1.31	-
*DW	71	64	-	2.41	2.10	-	1.11	1.04	-
*AW	81	68	-	4.61	3.97	-	2.77	2.27	-
MA	-	69	63	-	2.37	1.93	-	1.28	1.07
DD	70	79	-	2.49	2.49	-	1.42	1.45	-
MN	-	67	-	-	2.16	-	-	1.43	-
MEAN	64	64	61	2.66	2.53	2.46	1.50	1.47	1.45
±SD	7	7	6	0.76	0.62	0.89	0.48	0.34	0.49

* Group 2A

Table 7.50: SUBSET SERIAL ERECT RESTING RADIONUCLIDE DATA: (Mean ± S.D.)

	EF			PFR			ADFR		
	0	6	12	0	6	12	0	6	12
2A	65	65	58	2.82	2.61	2.60	1.53	1.52	1.62
	7	6	4	0.85	0.66	0.21	0.57	0.39	0.11
2B	64	64	63	2.36	2.48	2.41	1.47	1.43	1.39
	7	8	7	0.47	0.60	1.04	0.28	0.32	0.56

VII.5.3.7 Serial Erect Exercise Haemodynamics

Table 7.51 summarises the serial erect exercise haemodynamic data in the 26 patients studied. Similar to the supine posture, heart rate and cardiac index remained unchanged with similar mean values. In addition there was a progressive increase in peak exercise PCWP ($p < 0.01$), but lower values were recorded in the erect posture. Although SBP was higher during the supine posture, there was nevertheless a progressive increase in SBP over the twelve month period ($p < 0.01$).

When stratified into subsets (table 7.52) serial heart rates were similar in the two groups with a small but progressive rise in SBP which was consistently higher in the group 2B patients (219 $\pm$ 15 versus 209 $\pm$ 28mmHg).

As was also evident during supine exercise, exercise PCWP rose progressively with time, particularly in group 2A ($p < 0.05$), and was consistently higher in the group 2B patients ($p < 0.05$). Although 60% of group 2A patients (versus 78% during supine exercise) had a normal exercise PCWP at initial assessment, only 40% (versus 33% during supine exercise) had a normal value at 6 months, and no patient had a normal exercise PCWP at 12 month assessment. In contrast, approximately 1/3 of group 2B patients(versus 12% during supine exercise) had a normal exercise PCWP at initial and 6 month assessments, but similarly no patient had a normal PCWP at 12 months. Despite similar subset serial heart rate, SBP and exercise PCWP responses during the two exercise postures, cardiac index was consistently higher in the erect posture in the group 2A patients (11.0 versus 9.1L/min/M^2 at rest, $p < 0.05$), but with the mean values remaining essentially unchanged

over the assessment period.

Table 7.51: SERIAL EVALUATION OF ERECT EXERCISE HAEMODYNAMIC DATA:

	HR			SBP			CI			PCWP		
	0	6	12	0	6	12	0	6	12	0	6	12
*SA	170	182	-	170	190	-	10.1	8.7	-	10	12	-
LA	185	180	-	230	220	-	12.6	12.7	-	15	18	-
*SA	180	194	172	220	240	220	14.6	12.6	12.2	16	20	27
MB	170	155	-	230	210	-	10.6	10.6	-	19	25	-
AC	-	160	165	-	190	220	-	9.7	8.4	-	15	20
*DD	180	170	-	270	250	-	13.2	13.7	-	25	20	-
HH	170	174	180	250	250	270	9.8	10.2	10.6	15	25	20
*PJ	170	185	-	180	180	-	11.1	11.0	-	20	29	-
*JJ	180	170	-	210	195	-	12.3	8.5	-	18	21	-
*KK	170	172	180	220	250	220	9.9	12.8	11.4	15	28	22
GM	-	176	-	-	240	-	-	9.4	-	-	12	-
PM	-	150	168	-	200	200	-	10.7	9.3	-	22	25
*NO	160	140	150	210	250	230	10.4	11.6	11.0	6	15	18
MP	200	204	-	210	200	-	9.3	7.9	-	22	20	-
SR	145	158	-	220	230	-	7.3	8.8	-	25	33	-
WS	194	186	-	200	240	-	6.6	9.5	-	12	23	-
TS	182	175	-	200	210	-	7.2	8.7	-	30	30	-
FT	188	190	-	190	190	-	10.8	12.7	-	25	22	-
VdS	-	165	160	-	300	300	-	9.5	13.6	-	14	17
LV	-	170	170	-	270	280	-	15.7	12.3	-	21	25
*CV	180	174	-	220	200	-	-	11.5	-	15	12	-
*DV	140	130	-	190	210	-	10.6	14.0	-	13	10	-
*AW	200	180	-	200	190	-	6.4	7.5	-	12	17	-
MA	-	172	160	-	230	190	-	7.5	6.2	-	42	38
DD	180	150	-	240	210	-	8.1	9.9	-	26	15	-
MN	-	150	-	-	200	-	-	5.9	-	-	13	-
MEAN	176	170	167	214	221	237	10.1	10.4	10.6	18	21	24
±SD	16	17	10	24	29	38	2.3	2.3	2.3	6	8	6

* Group 2A

Table 7.52: SUBSET SERIAL ERECT EXERCISE HAEMODYNAMICS: (Mean ± S.D.)

	HR			SBP			CI			PCWP		
	0	6	12	0	6	12	0	6	12	0	6	12
2A	173	170	161	209	216	223	11.0	11.2	11.5	15	18	22
	16	20	16	28	24	6	2.3	2.3	0.6	5	7	5
2B	179	170	167	219	224	243	9.1	10.0	10.1	21	22	24
	16	16	8	15	30	46	2.0	2.3	2.7	5	8	7

VII.5.3.8 Serial Erect Exercise Radionuclide Data

The group data is summarised in table 7.53. As occurred during supine exercise, there was a slight but progressive increase in exercise capacity over the 12 month period. In contrast, at 6 month assessment, despite no change in exercise LVEF, there was a marginal fall in PFR (4.84 ± 1.43 to 4.39 ± 1.23 EDV/sec) and ADFR (2.41 ± 0.59 to 2.18 ± 0.72 EDV/sec) with a further significant fall in these measures at 12 months (PFR, $p < 0.05$; ADFR, $p < 0.01$). At that time exercise LVEF had dropped appreciably from 59 ± 13 to 52 ± 5% ($p < 0.05$).

A progressive improvement in exercise capacity by 1 level, occurred in 27% of group 2A and 21% of group 2B patients at 6 months. As occurred during supine exercise, group 2A patients had a significantly higher exercise LVEF ($p < 0.01$) and PFR ($p < 0.05$) with no patient at initial or 6 month assessment having an exercise LVEF < 50% (versus 4 of the group 2B patients). Peak exercise LVEF remained unchanged at 6 months in both subsets, with a significant drop in group 2A (66 ± 8 to 53 ± 6%, $p < 0.01$) at the 12 month assessment. This fall in exercise LVEF was associated with a progressive reduction in diastolic filling rates (PFR, $p < 0.05$; ADFR, p = NS).

Table 7.53: SERIAL EVALUATION OF ERECT EXERCISE RADIONUCLIDE DATA:

	EF			PFR			ADFR			Ex.Cap		
	0	6	12	0	6	12	0	6	12	0	6	12
*SA	64	60	-	4.05	3.86	-	1.99	1.78	-	550	550	-
LA	66	62	-	5.92	4.74	-	2.67	2.17	-	600	750	-
*SA	57	59	49	6.38	5.38	3.71	2.84	2.71	1.89	900	1050	900
*MB	67	61	-	5.08	3.21	-	2.41	1.65	-	750	750	-
AC	-	61	61	-	5.64	5.64	-	2.63	2.74	-	600	600
*DD	60	69	-	5.80	5.32	-	3.04	2.44	-	1050	1050	-
HH	52	55	48	4.14	4.60	2.48	2.20	2.29	0.95	600	600	750
*PJ	58	50	-	4.91	2.88	-	2.07	1.60	-	750	750	-
*JJ	72	72	-	5.69	5.34	-	2.14	2.43	-	900	750	-
*KK	55	66	57	4.70	5.54	4.46	2.66	3.15	2.35	600	750	750
GM	-	60	-	-	2.71	-	-	1.20	-	-	900	-
PM	-	61	44	-	3.92	3.75	-	2.23	1.71	-	750	750
*NO	61	71	-	2.29	3.20	-	1.43	2.07	-	900	900	1050
MP	-	83	-	-	6.78	-	-	3.76	-	600	600	-
SR	56	65	-	3.64	5.33	-	1.60	2.01	-	450	600	-
WS	35	46	-	-	4.46	-	-	2.13	-	600	600	-
TS	48	27	-	2.92	3.29	-	-	1.12	-	750	750	-
FT	45	26	-	3.81	2.84	-	2.13	1.49	-	750	900	-
VdS	-	48	50	-	3.68	2.95	-	1.44	1.37	-	1050	1050
LV	-	52	53	-	4.23	4.36	-	2.11	-	-	900	900
*CV	63	73	-	6.03	6.41	-	2.98	3.36	-	900	900	-
*DV	70	65	-	4.74	3.52	-	2.01	1.52	-	900	1050	-
*AW	77	81	-	8.27	6.05	-	3.68	3.69	-	350	350	-
MA	-	62	54	-	4.36	4.73	-	2.02	1.90	-	600	600
DD	52	57	-	3.94	-	-	2.41	-	-	600	450	-
MN	-	53	-	-	2.51	-	-	1.51	-	-	-	-
MEAN	59	59	52	4.84	4.39	4.01	2.41	2.18	1.84	708	756	817
±SD	10	13	5	1.43	1.23	1.01	0.59	0.72	0.59	187	197	170

* Group 2A

Table 7.54: SUBSET SERIAL ERECT EXERCISE RADIONUCLIDE DATA: (Mean ± S.D.)

	EF			PFR			ADFR			Ex. Cap		
	0	6	12	0	6	12	0	6	12	0	6	12
2A	64	66	53	5.27	4.61	4.10	2.48	2.40	2.12	791	805	900
	7	8	6	1.50	1.28	0.53	0.63	0.76	0.33	207	220	150
2B	51	55	52	4.06	4.22	3.99	2.20	2.01	1.73	690	718	775
	10	7	6	1.00	1.20	1.17	0.40	0.67	0.67	96	168	175

VII 5.4 SUMMARY OF SEQUENTIAL DATA

1. The clinical status of all patients evaluated remained unchanged over the 6 to 12 month study period.

2. Echocardiographically determined LV dimensions and systolic

function remained stable. However, 10 patients had a progressive rise in systolic wall stress.

3. There was a gradation in haemodynamic abnormalities with a progressive rise in both resting and exercise PCWP, an increase in exercise SBP and a reduction in resting cardiac index over time.
4. Although resting LVEF remained unchanged, there was a progressive increase in the number of patients with an abnormal LV functional reserve - this appeared to be associated with both a higher afterload (increased SBP) and increased diastolic stiffness (reduced peak and average diastolic filling rates).
5. Some patients (18%) showed a variable LVEF response to exercise on repeat resting.

CHAPTER VIII

DISCUSSION

VIII.0.0 INTRODUCTION

Each subsection of results will be discussed and this will be followed by an overall discussion and a reflection of the results.

VIII.1.0 CLINICAL CHARACTERISTICS

VIII.1.1 Demographic Data

It will be noted that the mean age of the two groups at the time of initial assessment was 32 years in the symptomatic group (range 14 to 66 years) and 24 years in the asymptomatic group (range 16 to 44 years). Although the symptomatic patients were slightly older, consistent with the natural history of the disease (Segal 1956, Rapaport 1975, Bonow 1983), the two groups are both young (< 35 years) and thus comparable, particularly in view of the clinical problem of the development of LV dysfunction before the onset of symptoms. In addition, being a disease of the young in our country, this highlights the problems of valve replacement surgery, particularly premature xenograft failure (Rose 1978, Thandroyen 1980, Curcio 1981), the ability to use anticoagulant therapy (geographical locality) and the devastating sequelae of central nervous system emboli (Stinson 1977, Cohn 1979). Although earlier valve replacement surgery may be recommended in an ideal society, imperfect valve design precludes this recommendation in our patient population and in most populations in which valvular heart disease is common.

The male preponderance was confirmed in the asymptomatic group (ratio 6:1), but the sex ratio was similar in the symptomatic patients. This is almost certainly a reflection of the fact that asymptomatic males are identified and referred at the time of pre-employment medical examinations. Furthermore, local demographic factors are of great importance. Males come to major cities for employment at a young age; females come when they become symptomatic.

VIII.1.2 Aetiology

Although acute rheumatic fever remains a major health problem in this country, only about half the patients evaluated had a history consistent with a previous acute attack, and in approximately 40% of the cases in both groups, the aetiology was unknown.

VIII.1.3 Symptomatology

The natural history of chronic aortic regurgitation is marked by a stable prolonged initial plateau phase and subsequent progressive deterioration (Goldschlager 1973, Rapaport 1975). Once signs and symptoms of congestive heart failure supervene, irreversible LV dysfunction may have occurred with a subsequent suboptimal surgical result (Clark 1980). There is, of course, a natural reluctance for clinicians to recommend open heart surgery in asymptomatic or minimally symptomatic patients; thus, in the practical management of patients with chronic severe aortic regurgitation, the clinician relies heavily on the detection of significant early symptoms. The evaluation and interpretation of these symptoms is highly subjective. Moreover, experience with patients has shown that symptoms do not always reflect underlying cardiac function (Patterson 1972, Franciosa 1979), other reports have shown a poor

correlation between LV size and symptomatic status (Borow 1980, Henry 1980) and more recently it has been established that long-term survival after aortic valve replacement is best predicted by the state of the LV systolic pump function (Greves 1981).

As it is our policy to advise aortic valve replacement at the earliest onset of symptoms, it will be noted that 87% of the symptomatic group were in NYHA functional class IIA and IIB (NYHA 1979). No patients were Class IV limited and only 3 patients (13%) were Class III. This is in accordance with the reported impression that surgery is being recommended earlier in the natural history of symptomatic chronic severe aortic regurgitation and appears to be associated with an improved late survival (Henry 1980, Turina 1984). However, two other studies showed that functional capacity alone did not correlate with the probability of survival (Samuels 1979, Cunha 1980), but when combined with LV ejection fraction Greves et al(1981) showed that 5 year survival of patients in functional Class III and IV improved from 63% to 90% if the LVEF was >0.50. Ten patients had a previous episode of congestive heart failure which responded well to therapy, with the majority in functional Class II at the time of assessment. The mean duration of symptoms was 16$\pm$4 months with a wide range from 1 to 130 months.

Although classical angina pectoris is a well known symptom in chronic aortic regurgitation, none of the study patients had effort-induced oppressive chest pain. However, 56% of the symptomatic group and 29% of the asymptomatic patients had transient, short-lived atypical left praecordial chest pain. Subsequent to completion of this study, one of the asymptomatic patients(J.J.) underwent succesful aortic valve replacement with

cessation of chest pain following two hospital admissions with severe chest pain unassociated with ECG change or a rise in cardiac enzymes. Coronary angiography had revealed normal coronary arteries. Nearly half the symptomatic group gave a history of short-lived, rapid, regular palpitations almost exclusively effort-related and unassociated with any other symptoms. Holter monitoring was not performed in any patients, but it is now appreciated that both pre-operative and particularly postoperative ventricular ectopy may be an important factor in the long-term outcome of these patients(Olshausen 1983, Olshausen 1984).

VIII.1.4 Clinical Assessment

All patients had the classical peripheral and auscultatory features of severe aortic regurgitation with a similarly wide pulse pressure in both symptomatic and asymptomatic groups. No patients were in congestive heart failure at the time of assessment and thus clinical features were not helpful in the stratification of patients in this study.

VIII.1.5 Electrocardiogram

Patients with chronic severe aortic regurgitation generally have hearts of greater weight than that observed in other conditions (Roberts 1985) and consequently have larger QRS voltages. Although QRS voltage criteria for LV hypertrophy are not always reliable (Scott 1960, Baxley 1968, Reichek 1981, Devereaux 1983), it remains an important and integral part of the clinical assessment. The Sokolow-Lyon index (1949), using the sum of the S wave in V_1 plus the larger of the R wave in either V_5 or V_6 of > 35mm, is the most widely used QRS criteria for LV hypertrophy. More recently, Roberts et al (1985) in a necropsy correlated study, reported the

usefulness of the total 12-lead QRS amplitude (normal < 175mm).

Voltage criteria for LV hypertrophy was fulfilled in 73% of necropsy patients using the Sokolow-Lyon index, compared to 90% using the total 12-lead QRS amplitude.

In my study, sinus rhythm was present in all patients, with all but 2 patients in each group (94% of the symptomatic and 93% of the asymptomatic patients) having LV hypertrophy with repolarisation change as assessed by the Sokolow-Lyon index. More specifically, 22/28 asymptomatic and 19/32 symptomatic patients had severe LV hypertrophy with LV voltage >60mm. All 4 patients with no electrocardiographic evidence of LV hypertrophy had an increased CSA on their echocardiogram.

VIII.1.6 Chest Radiograph

Cardiomegaly, as assessed by a cardio-thoracic ratio(CTR) >0.50 was present in all but 1 patient in the symptomatic group (mean 0.55$\pm$0.06) and in all but 4 patients in the asymptomatic group (mean 0.59$\pm$0.05). However, all 4 asymptomatic patients had mild to moderate LV dilatation on M-mode echocardiography (DED 5.9 to 6.7cm).

Although previous studies have reported the prognostic importance of the CTR in the late survival of patients with aortic valve disease (Chikos 1977, Hammermeister 1979), this variable did not appear to have important predictive value in my series. In addition, although a sudden, significant increase in CTR at follow-up assessment is used as an indication for aortic valve replacement, this phenomenon was not encountered in the 12 to 18 month follow up period of this study. However, it should be

appreciated that this was a relatively short-term evaluation.

VIII.2.0 INITIAL ASSESSMENT

VIII.2.1 M-MODE ECHOCARDIOGRAPHY

Chronic AR results in LV chamber dilatation and an increase in LV muscle mass. If the haemodynamic volume overload is gradual, compensatory myocardial hypertrophy develops and, even though LV diastolic volume and muscle mass may be increased, the ratio of EDV to muscle mass (V/M ratio) and peak systolic wall stress(PSWS) remain normal. Early in the evolution of these above changes, the contractile state of the myocardium remains normal with a preserved LVEF. Thus, compensated chronic AR typically produces LV chamber enlargement, a large LV stroke volume and normal systolic EF. It appears that the large stroke volume is maintained by virtue of a large end-diastolic volume with an increased number of sarcomeres around the circumference of the ventricle and normal shortening of each sarcomere (Ross 1974).

Eventually, compensatory hypertrophy may fail to keep pace with the volume overload (increased V/M ratio) with the resultant increase in systolic wall stress/afterload causing a decrease in fibre shortening by virtue of the inverse force/velocity relation. In contrast, if the quality of the hypertrophied muscle is abnormal, muscle shortening may decline in the presence of a normal afterload.

Thus, in the later stages of chronic AR, the systolic EF falls and the ESV increases; the LV diastolic pressure rises and the patient develops pulmonary venous hypertension and congestion. Unless

interrupted by aortic valve replacement, a vicious cycle follows, progressing to irreversible myocardial damage. Unfortunately, this unwanted end result may occur before the onset of significant symptoms, making optimal timing of aortic valve replacement difficult.

A major purpose of this study was to examine the predictive value of several pre-operative echocardiographic variables and these will be highlighted in the discussion of the sequential and postoperative results.

Against a background of the above knowledge, the results of this prospective study show that all but one asymptomatic and two symptomatic patients had LV dilatation manifested by increases in both end-diastolic and end-systolic dimensions determined echocardiographically. Left ventricular fractional shortening was normal in the majority of patients, being significantly reduced in only 1 symptomatic patient and borderline in 2 patients in each of the symptomatic and asymptomatic groups. Importantly, all the symptomatic patients in this subset had symptoms for less than 6 months. These findings are consistent with previous echocardiographic studies (Johnson 1976, Venco 1976, Gaasch 1978, Henry 1980, McDonald 1980, Stone 1984, Fioretti 1985).

The degree of LV dilatation was similar in the two groups of patients (DED 6.9$\pm$1.1cm symptomatic versus DED 6.8$\pm$0.9cm asymptomatic), although 5 patients (16%) in the symptomatic group in contrast to only 2 (7%) asymptomatic patients had marked LV dilatation (DED > 8.0cm). Although previously thought to be less predictive than the DES, it has recently been reported to be the best pre-operative predictor of persistent postoperative LV

enlargement (Fioretti 1985) - its importance in my study will be discussed in the postoperative and sequential assessments.

With regard to the DES, once believed to be predictive of a poor postoperative result (Borow 1980, Henry 1980), 25% of the symptomatic group had dimensions in this range (including 4 of the 5 patients with a DED > 8.0cm). Only 7% of the asymptomatic patients had a DES > 5.5cm. Two other studies (Turina 1979, Cunha 1980) failed to find any significant relationship between both late survival and late clinical results on the basis of LV dimensions obtained from pre-operative M-mode echocardiograms.

Numerous studies have highlighted the significant limitations of assessing LV size and function in patients with severe aortic regurgitation with the use of M-mode echocardiography (Johnson 1976, Abdulla 1980, O'Rourke 1980).

Normalisation of echocardiographic dimensions occurred in two-thirds of the subset of symptomatic patients who underwent aortic valve replacement and remained unchanged in the one symptomatic patient followed over a twelve month period.

A radius to wall thickness ratio of > 4.0, which reflects whether the degree of LV hypertrophy is appropriate for a given chamber volume, has been reported to identify patients with chronic aortic regurgitation who are at risk of persistent postoperative LV enlargement (Gaasch 1978, Gaasch 1983). This index is linearly related to the end-diastolic volume to mass ratio within a broad range of dimensions and mass and has been proposed to be independant of fractional shortening. Importantly however, the R/Th must be "normalised" for LV systolic pressure. The rationale

for pressure normalisation of R/Th rests in the relationship between wall stress and pressure, radius and wall thickness. Since the R/Th ratio at end-diastole is nearly equal to this ratio at the time of peak systolic stress (Grant 1965), the product of peak systolic pressure and the R/Th ratio provides an index of peak systolic stress. Peak systolic stress is known to be near normal in patients with chronic compensated heart disease (<55OmmHg) and increased (>6OOmmHg) in those with decompensated hearts (Grossman 1975, Gaasch 1979, Gaasch 1983). At initial assessment in my study, 3 symptomatic and 2 asymptomatic patients had a R/Th ratio > 4.O and a systolic wall stress of >6OOmmHg. All the symptomatic patients had an associated DES > 5.5 whereas neither of the asymptomatic group patients had an increased DES.

Following surgical correction of chronic aortic regurgitation some postoperative regression of left ventricular hypertrophy is common, although previous studies have reported a persistently increased LV mass in most patients (Kennedy 1977, Gaasch 1978, Pantely 1978, Schuler 1979, Clark 198O, Henry 198O). The causes of incomplete regression are not known, but include paraprosthetic regurgitation, systemic hypertension, patient-prosthesis mismatch and the amount of LV hypertrophy present pre-operatively may influence the extent of postoperative regression(Gaasch 1982). In a subset of 9 cases with incomplete regression in their series, the mean cross-sectional area (CSA) was $28 \pm 2 cm^2$. In my study a virtually identical number of patients in each group (11/28 symptomatic, 1O/28 asymptomatic) had a significant degree of left ventricular hypertrophy as assessed by an echocardiographic CSA > 3O.Ocm^2. In only one patient (M.B.) was it associated with an increased R/Th ratio and systolic wall stress, implying inadequate hypertrophy for

the massive LV dilatation in this man (DED 9.7cm, DES 7.7cm).

Although Starling's cardiac output curve (Guyton 1973) and the shortening velocity of the cardiac wall fibre (Braunwald 1976) are the two common techniques for assessing the contractile state of the heart, Sagawa et al (1977) proposed a third technique based on the time-varying systolic pressure/volume relation. They claimed that the ventricular pressure/volume ratio at end-systole was relatively insensitive to cardiac loading (a major limitation in the use of LVEF) and varied greatly in response to changes in ventricular contractility. Subsequent clinical reports (Nivatpunin 1979, Branzi 1984) showed that the peak LV systolic pressure/systolic volume ratio was more sensitive than ejection fraction in detecting subtle changes in myocardial function in humans.

A previous invasive study (Nivatpumin 1979) showed a curvilinear relationship between the plot of peak systolic pressure/volume ratio versus ejection fraction with a ratio of < 1 in patients with an LVEF < 40% and ranging between 1 and 5 in patients with an LVEF > 60%. Substituting fractional shortening for LVEF, my study confirms this curvilinear relationship with a lower ratio generally associated with a lower percentage fractional shortening. No case was associated with a ratio of < 1, although only one patient (M.L) had a fractional shortening of < 20%.

M-mode echocardiographic measurements of LV volume have been criticised because of poor correlation with angiographic values (Johnson 1976, Teichholz 1976, Abdulla 1980). This is born out in this study, particularly in the asymptomatic group where the echocardiogram consistently underestimated angiographic end-

systolic volume and thus further evaluation of this measure of contractility was not undertaken (symptomatic r = 0.87, asymptomatic r = 0.51).

VIII.2.2 EXERCISE EVALUATION

The data on LV performance during exercise in man are inconclusive and physical fitness, methodologic problems and body position during exercise account partialy for the inconsistency of these results.

VIII.2.2.1 Normal Values

In general, normal subjects have a significant increase in stroke volume on exercise (Wang 1960, Bevegard 1963, Epstein 1967) with variable changes in end-diastolic and end-systolic volume (Braunwald 1963, Weiss 1979, Poliner 1980). LV ejection fraction usually increases by at least 5% due to an increase in stroke volume that may be mediated by several mechanisms including a decrease in end-systolic volume, an increase in end-diastolic volume, an increase in end-diastolic volume greater than the increase in end-systolic volume and lastly an increase in end-diastolic volume with a decrease in end-systolic volume. From previous work it appears that both the Frank-Starling mechanism and an increase in LV contractility are important in augmenting the stroke volume in normal subjects (Poliner 1980, Iskandrian 1981). This change in LV ejection fraction has been widely used to characterise a normal versus abnormal response to exercise (Port 1980, Rerych 1980, Bar-Shlomo 1982). Importantly, it has recently been shown that patients with a high resting ejection fraction (> 70%) may not increase their ejection fraction on exercise (Poliner 1981, Wasserman 1984).

A previous non-invasive study evaluating patterns of LV diastolic filling in chronic aortic regurgitation (Lavine 1985), compared their results to a group of normal controls. The group comprised 24 subjects, with a mean resting peak filling rate of 3.09±0.71 EDV/sec and an ADFR (mean filling rate) of 1.63±0.29 EDV/sec.

In my group of normal controls the mean resting LV ejection fraction was 63±3% with a significant rise on exercise to a mean of 79±7%. In only one patient was there no significant increase in LV ejection fraction, and it will be noted that he had the highest resting value of 67% and probably represents a normal response in this subset(Poliner 1981, Wasserman 1984). Peak filling rate was 2.96±0.46 EDV/sec which is similar to the above study and ADFR was also in a similar range.

VIII.2.2.2A The Effects of Posture on Resting Haemodynamics and Radionuclide Data in Symptomatic and Asymptomatic Chronic Severe Aortic Regurgitation

The influence of posture on the haemodynamic and functional responses to exercise in normal persons (Poliner 1980, Manyari 1983) and in patients with coronary artery disease (Thadani 1977, Freeman 1981) are well described. In patients with chronic severe aortic regurgitation these effects should be particularly relevant because of the alterations in load and fluctuations in the degree of regurgitation. In a recent study of patients with moderate to severe aortic regurgitation (Shen 1985), posture was demonstrated to be important in determining the LV response to exercise, with exercise-induced LV dysfunction occurring significantly more often during supine than erect exercise. These workers recommended that comparisons not be made between different postures in individual patients and that because exercise-induced LV dysfunction occured

significantly more often during supine exercise, this position be used for assessing LV functional capacity in asymptomatic patients with aortic regurgitation.

This study of patients with chronic severe aortic regurgitation confirms that upright and supine body positions alter LV function at rest, with higher erect heart rate, lower erect systolic blood pressure and stroke volume index (forward flow) and significantly lower pulmonary capillary wedge pressure (PCWP). The increased heart rate is thought to be the result of increased sympathetic and reduced vagal tone (Gauer 1965) with the lower stroke volume occurring because of decreased LV preload. However, although cardiac index was significantly lower in the semi-erect posture in the symptomatic patients, with 41% having a reduced resting cardiac index(CI) <2.5 L/min/M^2 (compared to 16% in the supine posture), the CI remained unchanged during both postures in the asymptomatic group, with no patients having a reduced cardiac output. These results in the asymptomatic group are at variance with previous reports (Poliner 1980, Manyari 1983, Thadani 1977, Freeman 1981, Sheu 1985), and despite similar erect LV filling pressures to symptomatic patients, this group of patients was able to maintain a similar cardiac output.

Although PCWP was abnormal at rest in the supine posture in both symptomatic and asymptomatic patients, with only approximately 40% in each having a normal resting value of $<$ 15mmHg, it was markedly lower in the semi-erect posture with all the asymptomatic patients and 88% of the symptomatic group having normal resting semi-erect LV filling pressures.

The technique used for measuring pressure in the supine position in

our laboratory is from a zero reference level in the fourth right intercostal space and mid-axillary line. This zero reference level was not altered for measurements during semi-erect exercise. The mid-portion of the LV in the sitting posture often lies in the fifth or sixth intercostal space and it is possible that the pressures recorded from this chamber in the sitting position were minimally underestimated.

Left ventricular ejection fraction was similar at rest in both postures which is consistent with previous findings in normal subjects (Poliner 1980, Manyari 1983), but in contrast to the results reported in patients with AR (Shen 1985). Although almost one third of symptomatic patients had a reduced resting LVEF in both postures, only 7% of asymptomatic patients in the supine posture and none in the erect posture had an abnormal LVEF at rest. Thus, despite a decrease in preload, ejection fraction is maintained and may be due to a compensatory increase in contractility.

Although it would appear that both peak and average diastolic filling rates are higher in the erect posture in both groups, this may be a function of an increased heart rate rather than any other factor. In the supine posture however, both filling rates are significantly lower than controls which is in agreement with a previous study using gated blood pool scintigraphy to evaluate the pattern of diastolic filling in patients with moderate to severe aortic regurgitation (Lavine 1985). With virtually identical resting haemodynamics in the two groups in the supine posture, diastolic filling rates are similar, albeit marginally higher in the asymptomatic group.

VIII.2.2.2B Effects of Posture on the Exercise Haemodynamics and Radionuclide Data in Symptomatic and Asymptomatic Severe Chronic Aortic Regurgitation.

At peak exercise, corresponding to the same external workload during both postures, the heart rate, systolic blood pressure, stroke volume index and cardiac index achieved in each group was similar. However, to maintain the same cardiac index at peak exercise, the percentage increase in stroke volume index was much more marked in the erect posture, with a 43% increase in the symptomatic group and a huge 68% rise in asymptomatic patients. This is in agreement with the work of Thadani(1978) in normal subjects.

Peak exercise pulmonary capillary wedge pressure was lower in the erect posture, with a significantly smaller number of patients having an abnormal value (75% versus 90% in the symptomatic group and 52% versus 64% in the asymptomatic group). However, despite a normal or elevated PCWP during exercise, all the symptomatic and the majority of asymptomatic patients in this subset nevertheless had an abnormal LV functional reserve during both postures.

During exercise, mean LVEF decreased significantly in the supine posture with 81% of the symptomatic group having an abnormal LV functional reserve (Group 1B). In contrast, the fall in LVEF in the asymptomatic group was less, remaining normal at 57±12%, and with only 53% of patients having an abnormal LVEF response (Group 2B). These findings during supine exercise are in agreement with previous studies (Borer 1978, Dehmer 1981, Shen 1985). Contrary to the study by Shen(1985), LVEF also fell, although less significantly, during semi-erect exercise, with 75% of the symptomatic and 43% of the asymptomatic patients having an abnormal

LV functional reserve. These figures are only marginally lower than during supine exercise and refute the suggestion that changes in loading conditions and contractility during upright exercise may mask LV dysfunction in patients with chronic severe aortic regurgitation (Braunwald 1976, Lewis 1982, Shen 1985).

Although diastolic filling patterns in chronic aortic regurgitation have been reported at rest using ERNA, there are no reports to my knowledge of diastolic filling rates during exercise. The peak exercise heart rates were similar in the two groups during both exercise postures and therefore these values can be compared. The absolute values and incremental rise in both PFR and ADFR were higher during peak supine exercise in both groups, reflecting better peak and overall filling. Nevertheless, these supine values were significantly lower than in normal controls, with the asymptomatic group being two-thirds of normal and the symptomatic patients having values of approximately 50% of normal controls.

Several explanations are possible for the abnormal pattern of diastolic filling in these patients and include abnormal incremental elastance (a change in pressure divided by the change in volume at a common wall stress of 40Kdyne/cm^2 and ending when a 20ml/M^2 volume increase in the LV occurs, Rousseau 1982), simultaneous filling from the antegrade mitral and retrograde aortic flow (Lavine 1985) and abnormal stiffness (McCullagh 1972, Grossman 1974). Because volumes were not measured due to technical considerations and wall stress cannot be determined from radionuclide data, the role of incremental elastance could not be assessed. Similarly, radionuclide techniques cannot quantitate the extent and timing of antegrade or retrograde flow and thus the role

of diastolic regurgitant flow in altering diastolic filling patterns could not be evaluated. Finally, the role that abnormal LV chamber stiffness plays in chronic aortic regurgitation is not clear and does not correlate with peak filling rates (Magorien 1984).

Exercise capacity is used as a measure of cardiac reserve and also as a quantitative measure of functional class. Bonow and his group from the NIH(1980) showed that treadmill time did not correlate with echocardiographic dimensions and systolic function measured noninvasively. Many patients had a good effort tolerance despite a significant decrease in LV function, confirming the observation that patients with severe aortic regurgitation and left ventricular dysfunction may be asymptomatic. They showed that exercise capacity was an independent measure of cardiac reserve and a good predictor of normalisation of postoperative LV systolic function.

In my study, the normal controls averaged 6 levels or 18 minutes of supine and semi-erect, graded, symptom-limited, bicycle exercise with leg fatigue being the major limiting factor. This protocol conforms with the general principles of graded exercise testing which are well summarised by Bruce (1971). On an average, the exercise capacity in the symptomatic group was approximately 50% of normal controls, with dyspnoea the major limiting factor in the vast majority of cases. It is quite remarkable that almost half this group were able to tolerate an exercise PCWP ranging between 30 and 55mmHg. In sharp contrast, the exercise capacity in the asymptomatic group was almost 80% of normal controls, with leg fatigue the major limiting symptom. Only one-quarter of this group had a PCWP >30mmHg with a range of 30 to 38mmHg. Thus the ability

to tolerate an extremely high wedge pressure on exercise appears to be a major compensatory mechanism in chronic aortic regurgitation. Two mechanisms could have permitted this ability to tolerate the abnormally high pulmonary capillary wedge pressures: increased pulmonary lymphatic flow, allowing accelerated fluid removal (Uhley 1967) and chronic changes in capillary walls inhibiting transudation of fluid into the interstitium (Litchfield 1982). In addition, chronotropic competence (Eckberg 1971) contributed to our patients exercise tolerance.

VIII.2.2.2C Ejection Fraction Response to Supine Exercise in Symptomatic Aortic Regurgitation: Relation to Simultaneous Haemodynamics and Radionuclide Diastolic Filling

Since the demonstration by Borer et al (1978) that the left ventricular EF measured by ERNA may respond abnormally to stress in asymptomatic subjects with normal function at rest, this technique has received a great deal of attention. It has been heralded as a technique to identify a subset of patients with chronic aortic regurgitation (AR) who, despite normal resting LV function, have impaired LV functional reserve and are at risk for developing progressive LV dysfunction (Dehmer 1981, Bonow 1982, Lewis 1982, Huxley 1983, Iskandrian 1983, Johnson 1983). However, the determinants of the exercise EF response in chronic aortic regurgitation are complex and include changes in heart rate, regurgitant flow, preload, afterload and myocardial contractility. It would therefore appear to be overly sensitive, occurring very early in the natural history of chronic aortic regurgitation and there is growing evidence that exercise induced LV dysfunction is reversible (Bonow 1984, Gee 1985) and cannot be used to optimise the timing of aortic valve replacement.

Only limited data is available with regard to the haemodynamic correlates, particularly in symptomatic patients, and in some reports these were not simultaneously recorded (Boucher 1983, Massie 1985). In normal subjects, the haemodynamic response of the left ventricle to supine exercise is a small increase in stroke volume with either a drop, or at most, a 3mm increase in end-diastolic pressure.

In chronic volume overload as occurs in aortic regurgitation, the haemodynamic burden is complex, with both volume overload and a dynamic change in regurgitant volume. In addition, impaired cardiac function often does not result in distinct haemodynamic abnormalities at rest. In an attempt to better understand the LV ejection fraction response to exercise, Boucher et al (1982) correlated it with pulmonary capillary wedge pressure(PCWP) and found that only 40% of their overall group of patients had a normal exercise wedge pressure. They were able to show that this group generally had a higher resting and exercise LVEF with no significant change in ejection fraction on exercise. The majority (81%) of the symptomatic patients in my study had an abnormal LV functional reserve during maximal supine symptom-limited exercise (Group 1B). The small remaining subset (Group 1A) had an equivocal response with no patient displaying an EF increase of >5%. Importantly this equivocal or near/normal response occurred over a wide range of LV ejection fractions (LVEF 33 -76%), but those patients with a low resting LVEF < 50% had a slight drop in exercise LVEF, whereas those with an obviously normal value of >60% had a slight rise in EF. Two of this subset had resting ejection fractions of >70% and might thus not be expected to increase their LVEF further on exercise (Poliner 1981, Wasserman 1984).

The only differences at rest in these subsets was a higher and abnormal PCWP of 18±9mmHg in the Group 1B patients associated with significantly higher peak and average diastolic filling rates. In conjunction with the elevated PCWP, bigger end-diastolic volumes are postulated, which is confirmed by the echocardiographic measurement of a DEDI of 4.3±0.6 versus 3.9±0.8cm in the Group 1A patients. The improved diastolic filling in the Group 1B patients is unexplained and may merely reflect the small sample size (n = 6) with a near-normal functional reserve.

Although echocardiographic DESI, fractional shortening and R/Th ratio are similar in the two subsets, the end-systolic wall stress is slightly higher in the Group 1B patients (510±156 versus 434±21 in Group 1A, p = NS). Its significance is difficult to explain in the light of its role in limiting exercise in asymptomatic patients (vide infra) as Group 1B symptomatic patients had a better exercise tolerance than the Group 1A patients.

Despite a slightly lower resting LVEF in the Group 1A symptomatic patients (58±16 versus 63±10% in the asymptomatic Group 2A patients) resting haemodynamics and echocardiographic dimensions, resting %FS and wall stress are virtually identical. The only obvious difference is the peak and average diastolic filling rates, which are markedly lower and may reflect increased diastolic stiffness. However, these results should be interpreted with caution in view of the otherwise paradoxical finding of better diastolic filling in Group 1B patients and as mentioned, may just reflect the small number of patients in this subset.

The haemodynamic correlates at peak exercise are not comparable due to the rather surprising finding that the Group 1B patients had a

greater supine bicycle exercise tolerance. Thus, despite the normal LV functional reserve in a small number of symptomatic patients, their exercise capacity was only about 1/3 normal and about 50% of that achieved by asymptomatic patients with the same LVEF response. In addition, it was associated with a marked increase in PCWP and slower diastolic filling, albeit at a higher heart rate. Despite this, it is interesting to postulate that although the LV size, the degree of LV hypertrophy, the R/Th ratio and systolic wall stress at rest measured echocardiographically was the same in the symptomatic and asymptomatic patients, increased diastolic stiffness with a resultant significant increase in exercise PCWP and shortness of breath was the limiting factor in the exercise capacity of these patients.

VIII.2.2.2D Ejection Fraction Response to Supine Exercise in Asymptomatic Aortic Regurgitation: Relation to Echocardiography and Simultaneous Haemodynamic and Radionuclide Diastolic Filling Data.

In the asymptomatic patients in this study, the radionuclide findings are generally comparable with those previously reported (Dehmer 1981, Bonow 1982, Lewis 1982, Boucher 1983, Huxley 1983, Iskandrian 1983, Johnson 1983, Massie 1985). Approximately half the patients had a decrease in LVEF at peak supine exercise (Group 2B), with 13 patients having an equivocal or normal response (Group 2A). Once again, this latter response occurred over a wide range of resting ejection fractions and interestingly, two patients with a resting LVEF >70% had a significant rise on exercise (Poliner 1981, Wasserman 1984). In addition, contrary to a recent report by Massie et al (1985) in asymptomatic patients and my own symptomatic group, nearly one third of this subset had a normal LV functional reserve. This response has previously been noted but in a small

minority of patients and usually in those with only modest aortic regurgitation (AR). Although previous reports (Levinson 1970, Lewis 1970, Boucher 1983, Massie 1985) show that patients with asymptomatic AR have essentially normal haemodynamics at rest, approximately half this group in my series had elevated resting LV filling pressures with only about 60% of these falling into the subgroup with an abnormal LV functional reserve, i.e. 40% of patients with an abnormal PCWP at rest had a normal exercise LVEF response. No other haemodynamic differences were noted in the subgroups at rest.

Radionuclide determined PFR was marginally higher in the Group 2A patients and possibly reflects improved relaxation, associated with a normal resting PCWP and LV functional reserve.

Although radionuclide volumes were not determined, supine resting echocardiographic data and cardiac catheter volumes are available. When stratified on LV functional reserve, the echo DEDI was significantly higher in the Group 2B patients (4.5$\pm$0.4 versus 3.9$\pm$0.6cm in Group 2A, $p < 0.01$), with similar %FS (33$\pm$4 versus 34$\pm$4%) and R/Th ratio (3.1$\pm$0.6 versus 2.9$\pm$0.6). Although the volume to mass ratios were similar and within the normal range, resting systolic wall stress (SWS) was slightly higher in the group with an abnormal LV functional reserve (513$\pm$158 versus 417$\pm$90mmHg). A similar pattern is also evident in the symptomatic group, with virtually identical values to the two asymptomatic subgroups (see Appendix IV and V).

The difference in resting end-diastolic volume index at cardiac catherisation confirms the findings at echocardiography of increased LV dilatation in the subset of patients with a fall in

LVEF on exercise in both the symptomatic (203±63 versus 160±47ml/M^2) and asymptomatic groups (208±39 versus 172±13ml/M^2). As wall thickness could not be accurately measured in many patients, wall stress was not calculated.

The exercise capacity was similar in these two subsets of patients, but significantly higher than in the symptomatic group. This is in contrast to the study of Boucher et al (1983) who reported a correlation between the exercise LVEF response and exercise capacity. Cardiac index increased appropriately during exercise (3 fold increase) but in sharp contrast to normal subjects, exercise PCWP was abnormal in both subgroups, but significantly higher in those patients with a fall in exercise LVEF. Apart from being associated with an appreciable fall in LVEF, it was also associated with lower peak and average diastolic filling rates. The slightly higher peak exercise heart rate may be partially responsible for this observation, but increased diastolic stiffness is an alternative explanation. It will nevertheless be remembered that leg fatigue rather than breathlessness was the major limiting symptoms in the asymptomatic patients with chronic severe AR.

Although a recent study by Massie (1985) found that the EF response to supine exercise correlated closely with the exercise-induced increase in cardiac index ($r = 0.81$, $P < 0.001$) and significantly, though less closely and in an inverse manner with the increase in PCWP ($r = -0.69$, $p < 0.01$), this was not the experience in an earlier study by Boucher et al (1983). However, in this latter study, exercise radionuclide and haemodynamic measurements were not simultaneously obtained. Nevertheless, my study similarly found no significant correlation between the change in exercise EF and

changes in cardiac index, pulmonary capillary wedge pressure or peak diastolic filling rate, and thus its usefulness in the management of these patients is questionable. The mechanism responsible for the variable exercise LVEF response in patients with chronic severe AR is uncertain. These findings are not surprising in view of the known limitations of this dimensionless measure of LV function. The LVEF is altered in a complex fashion by changes in heart rate, loading conditions and contractility and is only a net measure of a number of factors, some of which serve to increase and others to decrease LV function. When LV preload is reduced or afterload is increased, EF may fall. Although earlier reports suggested that the abnormal EF response was the result of a decrease in LV preload (EDV) caused by a shortened diastolic filling period and a decrease in regurgitant volume secondary to an increase in heart rate (Judge 1971, Steingart 1983), more recent work has shown a variable change in EDV during exercise in these patients (Dehmer 1981, Peter 1982, Johnson 1983). In my study, preload, as reflected by the PCWP,increased in both subgroups (Group 2B > Group 2A) on exercise, with resting values also higher in the Group 2B subset. However, the PCWP may not be a true measure of preload(EDV) when the diastolic compliance of the LV is abnormal.

However, at rest, end-systolic wall stress, which is a measure of LV afterload, was higher in the group 2B patients (513$\pm$158 versus 417$\pm$90mmHg). Although stress was not measured during exercise, one of its direct variables, namely systolic blood pressure, rose considerably higher in the Group 2B patients (248 $\pm$30 versus 219$\pm$ 21mmHg). The other two variables, namely end-systolic volume and wall thickness, were not measured during exercise, but resting

values were similar in the two subgroups. Thus, the higher levels of resting wall stress suggest an important role of afterload excess in the LV functional reserve of patients with asymptomatic severe AR. This observation is in agreement with other reports (Osbakken 1981, Lewis 1982, Reichek 1982, Iskandrian 1983, Greenberg 1985, Kawanishi 1986). The fact that resting LVEF was normal despite higher SWS implies adequate basal reserve mechanisms which are exhausted when demands on the ventricle increase during exercise. Recent reports (Kumpuris 1982, Gaasch 1983) have also highlighted the prognostic significance of an abnormally high pre-operative SWS - this issue will be addressed in the discussion of my postoperative results.

It has been suggested that SWS is the stimulus for compensatory hypertrophy of the LV (Grossman 1975). To maintain SWS in the same range as those patients with a normal LV functional reserve, cross-sectional area(CSA) as a measure of LV hypertrophy, should have been and was significantly higher as these patients had more LV dilatation (CSA 31 ± 6 versus $26\pm6 cm^2$, $p < 0.01$). Whether this imbalance between load and hypertrophy was secondary to a gradual failure to develop adequate hypertrophy is therefore unlikely and the role of a change in the severity of regurgitation or a reduction in myocardial contractility cannot be answered from the available data.

Other factors known to influence the ejection fraction response to exercise, namely age (Port 1980, Rodeheffer 1984) and the presence of associated coronary artery disease were not issues in this study as the majority were young patients with a mean age of 24 years (range 16 to 44years) and all patients had normal coronary

angiograms. Although cuff systolic pressure rather than end-systolic pressure was used to calculate SWS, it has been found to closely correlate with end-systolic pressure in normal patients and in patients with heart disease, including aortic regurgitation (Grossman 1977, Bonow 1982, Reichek 1982).

Thus these findings confirm other published results (Hochreiter 1982, Lewis 1982, Iskandrian 1983, Goldman 1984, Greenberg 1985) that in the group of asymptomatic patients with preserved resting LV function there exists a subset with an elevated resting SWS. In my study, these patients had a resting SWS > 450mmHg, which appears to rise substantially on exercise and is associated with a drop in exercise LVEF. It would thus appear that afterload in excess of available myocardial reserve is an important determinant of this response.

In addition, lack of adequate hypertrophy to normalise wall stress and increased diastolic stiffness both at rest and on exercise (vide supra) suggest the failure of compensatory mechanisms. This impaired haemodynamic response to supine exercise may thus represent an intermediate stage between well compensated AR and the onset of overt LV dysfunction. Two recent studies (Bonow 1983, Huxley 1983) have shown that these patients do not have improved exercise responses over time and that they are at increased risk of becoming symptomatic and developing progressive deterioration of rest LV function. This issue will be addressed in my discussion on sequential evaluation.

Nevertheless, there is no evidence to suggest that this abnormal LV functional reserve is an indication for aortic valve replacement since patients under close follow up who exhibit functional

deterioration or develop symptoms have excellent surgical results (Henry 1980, Bonow 1984). The important implication is that patients with exercise induced LV dysfunction deserve careful and close follow up.

In the light of the fact that afterload excess may be an important factor in the apparent deterioration of LV performance, an important and as yet unanswered question is whether the early use of vasodilators would significantly alter the natural history of severe AR, thus delaying the need and hazards of valve replacement surgery. At present there is evidence in the short term that arterial dilating agents will reduce both LV volume and systolic pressure (Greenberg 1981), two of the important determinants of systolic wall stress.

VIII.2.2.2E Ejection Fraction Response to Erect Bicycle Exercise in Symptomatic Aortic Regurgitation: Relation to Simultaneous Haemodynamics and Radionuclide Diastolic Filling Rates.

Several studies utilising upright bicycle exercise have found that resting LVEF was similar and the EF response to upright exercise was generally a >5% increase in both asymptomatic and symptomatic patients. Because of this discrepancy in LV functional reserve between the two postures, it has been recommended that the EF response in one posture during exercise should not be applied to another (Iskandrian 1981, Lewis 1982, Marx 1982).

In addition, changes in posture significantly alter the haemodynamic profile, with resting values for end-diastolic pressure, PCWP, cardiac index and stroke volume index being significantly lower and heart rate higher in the erect position (Wang 1960, Bevegard 1963, Tuckman 1966). During upright exercise,

changes in EDV may be variable with either a decrease due to a reduction in regurgitant volume secondary to a shorter diastolic filling time (Iskandrian 1981), or an increase in EDV. During leg exercise, the blood pooled in the dependant region is shifted centrally by sympathetically mediated vasoconstriction and the action of the muscle pump(Clement 1976). However, because this marked enhancement of venous return is independant of posture, similar levels of EDV are expected during both body positions on exercise (Marx 1982, Shen 1985). Pulmonary capillary wedge pressure also increases but should normally not exceed 15mmHg(Ross 1966, Braunwald 1969, Rahimtoola 1975). Although it has recently become appreciated that only about 40% of asymptomatic or minimally symptomatic patients have a normal exercise PCWP in the supine posture (Boucher 1983), the response to upright exercise is not well reported. Similarly, diastolic filling patterns have, to my knowledge, not previously been described in patients with chronic severe aortic regurgitaion during upright exercise - with the increased EDV and reduced diastolic filling period, the expected response would be more rapid filling to accommodate this increased volume.

Contrary to the earlier reports (Iskandrian 1981, Lewis 1982, Marx 1982), my study shows that a similar proportion of symptomatic patients demonstrated an abnormal LV functional reserve to upright bicycle exercise (75% versus 81%). Despite a poor correlation between a normal erect and supine LV functional reserve, 10 of 12 or 83% of patients had an abnormal LV functional reverse in both erect and supine postures. Once again it is evident that a normal LVEF response to exercise occurred over a wide range of resting ejection fractions.

The resting haemodynamic profiles were identical in the two subsets and in agreement with previous reports on the changes in the upright posture (Wang 1960, Bevegard 1963, Tuckman 1966). In sharp contrast however, peak and average diastolic filling rates during the resting phase of upright bicycle exercise are significantly higher in the group 1A patients at similar heart rates and PCWP and although this may thus reflect improved relaxation in this subset, I caution this conclusion because of the small sample size (n = 4).

At peak exercise, the external workloads are dissimilar making direct comparisons difficult. In individual patients, the maximum workload achieved was the same as during supine exercise, with the order of body position during bicycle exercise not randomly allocated. Nevertheless, the haemodynamic profile in both subgroups was similar apart from a significantly higher systolic BP in the group 1B patients which is similar to the findings during supine exercise. As was evident at rest, at similar peak exercise heart rates and PCW pressures both peak and average diastolic filling rates were again significantly higher in the group 1A patients. Although one could postulate that systolic wall stress (afterload) was lower in this group and important in modulating the ejection fraction response to exercise, it would appear that improved diastolic filling during the upright posture may also play a role. Further studies will need to be done to evaluate this observation.

VIII.2.2.2F Ejection Fraction Response to Erect Exercise in Asymptomatic Aortic Regurgitation: Relation to Simultaneous Haemodynamics and Radionuclide Diastolic Filling Rates:

Although it is interesting to evaluate the exercise response in symptomatic chronic aortic regurgitation, the management of these

patients is generally straightforward. A far more problematic group are asymptomatic patients with chronic severe aortic regurgitation and significant LV dilatation. It is in this group that non-invasively determined prognostic markers are of crucial importance in the optimal timing of valve replacement surgery.

As occurred in the supine posture, a far more even spread of patients occurred in this group when divided according to their LV functional reserve. Thirteen patients formed group 2A and 10 patients group 2B. Nine of the thirteen Group 2A patients (69%) in the asymptomatic group had the same erect and supine exercise LVEF responses. Eighty percent (80%) of the group 2B asymptomatic patients had the same response, which is similar to the proportion of symptomatic group 1B patients. As occurred in the symptomatic group, the resting haemodynamic profiles in the two subsets of asymptomatic patients were virtually identical, but heart rate was higher and PCWP significantly lower than in the supine posture. A similar pattern of improved diastolic filling is noted in the group 2A patients in the erect posture at rest. Although the maximum external workload achieved was once again dissimilar, a number of important differences were noted.

Although systolic BP and PCWP were significantly higher in the group 2B patients during supine exercise, there is only a marginal difference in both these haemodynamic parameters at peak exercise in the erect posture. Cardiac index was significantly higher at an equivalent heart rate in the group 2A patients, implying improved forward flow. Since two of the variables of the systolic wall stress equation, namely systolic pressure (cuff BP) and end-diastolic volume (in this study PCWP was used as a measure of EDV)

are not grossly dissimilar in the two subgroups, by inference, a marked rise in SWS is probably not the operative mechanism in determining the EF response to erect bicycle exercise in asymptomatic patients with chronic severe AR. However, there is a marked difference in diastolic filling rates with much more adequate relaxation in the subgroup with a normal LV functional reserve. This difference cannot be ascribed to alterations in heart rates. Whether the improved forward flow and normal LV functional reserve in this subset of patients is due to systolic-diastolic interdependance (Bonow 1981, Polak 1982, Bahler 1983) or volumetric change secondary to improved relaxation is uncertain.

Thus it would appear from this study, in contrast to the report by Shen et al (1985), that exercise posture is not important in the stratification of asymptomatic patients on the basis of LV functional reserve. Upright exercise, being more physiological and more closely mimicking normal daily activity, should be the posture of choice in the evaluation of these patients. In addition, although afterload excess is the predominant mechanism responsible for the abnormal functional reserve during supine exercise, diastolic relaxation appears to be an important mechanism in the upright posture.

VIII.2.2.2G The Role of Isometric Exercise in the Evaluation of LV Performance in Chronic Severe Aortic Regurgitation:

In contrast to the sympathetically mediated increase in heart rate and contractility during dynamic exercise (Crawford 1979, Stratton 1983), a significant increase in systemic pressure is the most marked haemodynamic change during isometric handgrip exercise. However, there appears to be a great individual variation in the blood pressure response to isometric stress (Alain 1937, Chaney

1983). Many variables affect the increase in BP and include the intensity of the stress (Mitchell 1974), age (Kino 1975), sex (Petrofsky 1976), systemic hypertension (Lamid 1973) and heart disease (Fisher 1973). Although no increase in LVEDP is noted in normals (Helfant 1971, Kivomitz 1971), LV filling pressure commonly rises during isometric exercise in patients with chronic AR (Osbakken 1981). It has been postulated that the preservation of exercise capacity in chronic AR during isometric exercise is related to this elevation in LVEDP with a resultant decrease in regurgitant volume (Gerson 1984).

Nevertheless, despite certain theoretical advantages including its ability to provoke afterload mismatch (Ricci 1982) and evoke a greater elevation of LVEDP, numerous disadvantages (Gorlin 1957, Ellestad 1969, Atkins 1971) preclude its use in the routine non-invasive evaluation of LV functional reserve. However, recent studies (Gordon De Puey 1984, Shen 1985) have found that it may be a useful method for detecting LV dysfunction in patients with AR when adequate bicycle exercise cannot be accomplished.

In contrast, in my study using a standard protocol, there was minimal change in the haemodynamic and radionuclide systolic and diastolic profiles from the resting values in both symptomatic and asymptomatic patients with chronic severe AR. When patients were stratified according to their LVEF response to supine dynamic exercise, despite a modest increase in systolic BP (mean range 9 to 14mmHg), minimal change in the other variables was again noted.

It would thus appear from my study that, contrary to earlier reports (Paulsen 1981, Gumbiner 1983, Gordon De Puey 1984, Shen 1985), some of which were inhomogeneous with regard to the severity

of the AR and in general were conducted on small numbers of patients, isometric handgrip is a poor form of exercise in patients with chronic severe AR and measurements obtained in this way did not differ appreciably from resting haemodynamics or radionuclide ejection fraction or diastolic filling rates. It can thus not be recommended for use as an alternative to dynamic bicycle exercise.

VIII.2.2.2H The Value of Equivalent Workload Assessment in Symptomatic and Asymptomatic Severe Aortic Regurgitation:

Although it is well known that exercise type and body position may significantly influence the circulatory responses to exercise, the intensity of exercise has also been cited as important in uncovering mild to moderate degrees of functional impairment (Epstein 1969, Brady 1980, Jones 1981).

In an attempt to better evaluate the patterns of change in haemodynamic and radionuclide measurements and to possibly better explain the limiting factors to exercise in both symptomatic and asymptomatic severe AR, numerous variables were examined at equivalent workloads for the first three levels of supine bicycle exercise. This graded exercise protocol conforms with the general principles of effort stress testing in several ways, including: (i) exertion was initially submaximal, (ii) increments of work output were small, (iii) each stage was of sufficient duration to allow physiologic adaptation, (iv) the work was familiar to most patients, and (v) exercise was terminated for patient specific factors (Bruce 1971).

As has been previously noted, resting values in the two groups were similar although the LVEF at rest was slightly lower in the

symptomatic group (57 ± 12 versus 62 ± 8%).

During the first level of exercise, an abnormal LV functional reserve was present in 61% of the symptomatic group and only 32% of asymptomatic patients. The other significant difference was a 59% incremental rise in PCWP in symptomatic compared to 24% in asymptomatic subjects. However, although the incremental changes in diastolic filling were similar, both peak and average diastolic filling rates were appreciably higher in the asymptomatic patients at a similar heart rate and lower PCW pressure (EDV). Thus, although it would appear that at a low workload, significant volumetric changes, particularly in end-diastolic volume (preload) associated with an elevated PCWP and systolic wall stress (afterload), are responsible for the abnormal LV functional reserve seen in many of the symptomatic and some of the asymptomatic patients, the role of impaired relaxation cannot be discounted.

At an external workload of 300 kilo-pond meters/minute (level 2), a slightly bigger percentage of symptomatic patients (69%) but an appreciably higher percentage of asymptomatic patients (50% versus 32% at level 1) had an abnormal LV ejection fraction response to supine bicycle exercise. This was associated with a similar incremental rise in heart rate and cardiac index, a higher SBP and a significantly higher PCWP in the symptomatic group. Thus a significant increase in PCWP (and presumably EDV) and systolic wall stress (afterload) may once again explain the fall in EF in the symptomatic group but not in the asymptomatic group. Here the drop in exercise ejection fraction in nearly half this group was associated with a much lower PCWP and SBP. Diastolic filling rates were similar in the two groups. Thus a reduced preload and/or a

decrease in contractility at this modest workload may explain the drop in EF.

Although a slightly bigger percentage of symptomatic patients (76% versus 69% in level 2) demonstrated an abnormal LV functional reserve during the third level of supine bicycle exercise, the number of asymptomatic patients remained constant. Incremental changes in heart rate, SBP and cardiac index were again similar, but the symptomatic group once again had appreciably higher PCW pressures, although unchanged from level 2. When the symptomatic group were stratified according to LV functional reserve, PCWP was lower and filling rates higher in the group 1A patients. Thus, although increases in end-diastolic volume and systolic wall stress once again appear to be the operative mechanism in the symptomatic subset with an abnormal LV functional reserve, abnormal diastolic stiffness may be a contributing factor.

In the asymptomatic group as a whole, it will be noted that at the same external workload (450k-p.m./min), heart rate, PCW pressure and SBP are lower with a higher overall LVEF and significantly better diastolic filling. On stratification, group 2A asymptomatic patients had an appreciably lower PCWP and better diastolic filling rates. This superior diastolic filling, together with a lower afterload, may explain the better LV functional reserve and improved exercise capacity in asymptomatic patients with chronic severe aortic regurgitation. Why its influence only becomes apparent at this level of exercise in unexplained.

Thus, in summary, there appears to be a progressive increase in the number of patients with an abnormal LV functional reserve with increasing levels of exercise. However, in the symptomatic group,

the greatest increment (61%) occurs during the first level of exercise with only a small further increase to 76% during level 3. In contrast, in the asymptomatic patients, although only approximately 1/3 had a fall in LVEF during the first level of exercise, there was a progressive increase in this proportion during level 2 to 50% and then a plateau. Secondly, significant PCWP(and presumably volumetric) changes occurred early during supine bicycle exercise, particularly in the symptomatic group, and then appeared to plateau. Thirdly, although increases in EDV and systolic wall stress (afterload) appear to be the overriding mechanism for an abnormal LV functional reserve in symptomatic patients, diastolic stiffness may play an important role in the functional response of asymptomatic patients. Finally, from this data it would appear that low level exercise (1 to 2 levels) is adequate to stratify patients on the basis of LV functional reserve, accepting the fact that exercise capacity has been proposed as an important and independant marker for success following aortic valve replacement.

VIII.2.3. CARDIAC CATHETERISATION:

It will be noted that in the majority of reports concerning aortic regurgitation, cardiac catheterisation was not performed in many and in only some of the patients in other studies. In my series of 60 cases, all patients underwent complete right and left heart catheterisation and left ventriculography, aortography and coronary angiography so as to verify the severity of the aortic regurgitation and exclude associated valvular or coronary artery disease. Thus abnormal haemodynamics and contractile function were due solely to chronic severe aortic regurgitation and its effects on LV function.

The vast majority of symptomatic patients (87%) in my study were in NYHA functional class II. Only 3 patients were class III limited and thus this group (n = 32) has been considered as a whole and compared to the asymptomatic group (n = 28).

In aortic regurgitation, the need for an acceptable forward cardiac output requires an abnormally large stroke volume to compensate for the regurgitant volume which may be as high as 75% of the total LV stroke volume (Morrow 1965). The large stroke volume results in an increase in systolic blood pressure while regurgitation through the incompetent aortic valve produces a lowered aortic diastolic pressure. The amount of regurgitation is dependent on the orifice size of the aortic valve, the length of diastole and the pressure difference between the aorta and the left ventricle.

Although an appreciable number of both symptomatic and asymptomatic patients in my study had an aortic diastolic pressure higher than the reported literature, it should be noted that this finding is nevertheless consistent with severe AR. It did not relate to a change in systemic vascular resistance, but was rather associated with a significantly higher aorta to left ventricular pressure difference ($p < 0.01$), a major determinant of the severity of the regurgitation.

Chronic LV dilatation is essential and may be associated with different diastolic patterns of accommodation to the increased diastolic volume. In some patients, an increased LV end-diastolic pressure develops as if a normal diastolic pressure - volume curve was operative. In contrast, a second group displays apparent stress relaxation in diastole and appears to have better mechanical LV performance after surgery (Gault 1970).

Previous data evaluating the influence of LV end-diastolic pressure on late results after aortic valve replacement in severe aortic regurgitation are inconsistent (Hirshfeld 1974, Samuels 1979) and its influence on outcome in patients undergoing aortic valve replacement in this study will be discussed in the postoperative assessment. With regard to LV filling pressure measured indirectly by pulmonary capillary wedge pressure and directly by LV end-diastolic pressure in my study, the correlation was reasonably good in the symptomatic group ($r = 0.76$) but only moderate in the asymptomatic patients ($r = 0.60$). The explanation may lie in the variable left atrial booster pump function in patients with altered LV diastolic properties (Braunwald 1961, Rahimtoola 1975). The symptomatic group had both an abnormal pulmonary capillary wedge pressure of 16 $\pm$ 7mmHg, with 41% of patients having a value of $>$ 15mmHg, and an elevated LV end-diastolic pressure of 19 $\pm$ 8mmHg with 66% having an abnormal value of $>$ 15mmHg. In contrast, the asymptomatic group had a normal pulmonary capillary wedge pressure (13 $\pm$ 3mmHg) and LV end-diastolic pressure (15 $\pm$ 5mmHg) with only 14% having an abnormal wedge pressure. However, only 3 patients had a left ventricular end-diastolic pressure greater than 20mmHg compared to 10 of the symptomatic group. Thus the correlation in the symptomatic group may be due to higher and less variable PCW pressures.

In addition to higher filling pressures, the symptomatic group also had a lower mean cardiac index (3.2 $\pm$ 0.9 versus 3.9 $\pm$ 0.9L/min/M^2) measured by the indicator dye dilution technique (Hamilton 1948), with 16% (5 patients) having values of $<$ 2.5L/min/M^2. All these had evidence of significant resting LV dysfunction with associated elevation of LV end-diastolic pressure (range 20-40mmHg, mean

31mmHg). In contrast, no asymptomatic patient had a reduced resting cardiac index.

The thermodilution technique first introduced by Fegler in 1954 has been widely used for the measurement of cardiac output and previous reports have demonstrated a close agreement between thermodilution and dye dilution techniques in haemodynamically stable patients(Ganz 1971, Weisel 1975). However, there has been disagreement as to whether left-sided regurgitation renders the dye dilution technique inaccurate(Rahimtoola 1965, Samet 1966). It has been suggested that the distortion of the dye curve, with a resultant miscalculation of cardiac output (an approximately 20% underestimation), is caused by recirculation of indicator in the coronary arterial system. Samet(1966), and more recently Hillis et al(1985), have shown that right-sided injection and sampling of "cold" yields a curve less subject to recirculation-induced distortion in patients with AR and is preferable to dye and left-sided sampling. In comparing the cardiac output at catheterisation with that obtained during the resting phase of the exercise evaluation using the thermodilution technique, our series showed poor correlation coefficients of 0.37 in the symptomatic group and 0.15 in the asymtomatic group. An underestimation of cardiac output by the dye dilution technique occurred in 32% of the symptomatic group and only 14% of the asymptomatic subjects. Similar cardiac outputs by the two dilution techniques were recorded in approximately 40% in each group with an overestimation by the dye technique in half the asymptomatic patients but in only one quarter of the symptomatic group. This discrepancy between these two techniques should not detract from the results as only the thermodilution method was used in the exercise evaluation. The

protocol followed was that previously reported by Elkayam et al (1983), namely a 5ml injectate at O °C, taking the mean value of the second, third and fourth consecutive cardiac output measurements. We consistently found that the first reading was not accurate and may be related to the temperature of the catheter's contents after a long pause and on-going graded exercise; this was particularly found during the staged exercise measurements. No obvious explanation for this observation has been found and none of the factors operating in critically ill patients were identified (Ganz 1971, Wessel 1971, Weisel 1975, Snyder 1976).

The LV end-diastolic volume index (LVEDVI) was markedly elevated (normal LVEDVI 70 ± 20ml/m^2, Dodge 1983) in both groups with mean values of 193 ± 63ml/m^2 in the symptomatic group and 194 ± 47ml/M^2 in the asymptomatic patients. In this latter group, this large end-diastolic volume was associated with a normal or near normal LV end-diastolic pressure in the majority of cases, whereas in nearly half the symptomatic group the LV end-diastolic pressure was significantly elevated > 20mmHg. The considerable increase in LVEDVI in both groups serves to confirm that all the patients evaluated had significant longstanding aortic regurgitation. Gault et al(1970) described a rightward shift of the left ventricular pressure volume curve in patients with chronic volume overload and it is possible that this phenomenon was responsible for the large volume - low pressure status of the left ventricle in the majority of asymptomatic and some of the symptomatic patients and is the reason why you cannot equate PCWP and LV end-diastolic volume in these patients.

Similarly, end-systolic volume index was markedly elevated (normal

LVESVI 24 ± 10ml/M^2, Dodge 1983) in both groups but surprisingly it was higher in the asymptomatic group (mean LVESVI 111 ± 12ml/M^2 versus 88 ± 9ml/M^2 in the symptomatic patients). The probable explanation is the fact that 3 of the symptomatic group had near-normal LV volumes despite symptoms but, with only one patient(P.P) having an elevated LV end-diastolic pressure. A previously poor predictive value has been reported for angiographically derived LV volumes (Greves 1981). Both groups had similar resting LV ejection fractions (LVEF) measured angiographically using the area-length method (LVEF 0.54 ± 0.12 symptomatic versus LVEF 0.56 ± 0.09 asymptomatic, Dodge 1960). Although 28% of the symptomatic group had abnormal resting values of < 0.50, only 18% of the asymptomatic patients had reduced systolic pump function. In the symptomatic group, half the patients (n = 9) had severe LV dysfunction with associated elevation of LV end-diastolic pressure > 20mmHg and reduced resting cardiac index < 2.5L/min/M^2. In contrast, the subset of asymptomatic patients with abnormal LV contractile function (n = 5), all had a normal resting cardiac index with only 2 of the group having an obviously elevated LV filling pressure. Both these subset were associated with marked LV dilatation. It would thus appear that in symptomatic patients with reduced resting LV systolic pump function, approximately half the patients will have added haemodynamic evidence of significant LV dysfunction with a reduction in cardiac index and an elevation of LV filling pressure.

As will be noted from the angiographic data, all patients had qualitatively graded severe (3 to 4+) aortic regurgitation (Sandler 1963, Hunt 1973). More recently Croft et al (1984) have reported that the angiographic grading of regurgitation was often at

variance with the measured regurgitant volume index, particularly in patients with LV cardiomegaly. In patients with an LVEDVI > 120ml/M^2, angiographic grading of regurgitation was particularly likely to underestimate the regurgitant volume index, calculated by subtracting forward cardiac index from angiographic cardiac index. This was particularly true in patients with 3+ and 4+ regurgitation who, on the basis of qualitative assessment, might be recommended for aortic valve replacement. They suggested that a quantitative assessment be performed before surgical therapy is recommended.

In this regard, several methods of varying sophistication and reliability have been described (Sandler 1963, Hunt 1973, Lam 1981, Frank 1966, Clobanu 1982), including methods using electromagnetic flowmeters (Mennel 1972) and catheter-tip velocity transducers(Nichols 1981). However, many of these techniques require specialised equipment, are tedious and time-consuming, thus precluding their widespread use. Only one previous study (Hunt 1973) had compared the angiographic grading of aortic regurgitation with the regurgitant volume index, an accurate and widely used measure of valvular regurgitation (Hunt 1973, Sorensen 1980, 1982). In addition, relatively little attention has been given to the magnitude of the regurgitant volume itself, which is indeed the basis for both the haemodynamic abnormality and the clinical syndrome, with elimination of the regurgitant volume being the primary effect of successful valve replacement. Levine and Gaasch (1983) have proposed that there are convincing conceptual reasons and some experimental data to indicate that the ratio of regurgitant volume to end-diastolic volume is the major determinant of the ventricular response to surgical correction of chronic aortic regurgitation. Although in isolation it may not optimise

the timing of valve replacement, its sequential non-invasive evaluation (Sorensen 1980, Konstam 1981, Urquhart 1981) and the determination of when the product of systolic EF and regurgitant fraction (by substitution equal to the ratio of regurgitant volume to end-diastolic volume) begins to fall, may help time aortic valve replacement.

Using the angiographically derived regurgitant fraction (ratio of regurgitant volume to total stroke volume) rather than the regurgitant volume index, the mean value in the symptomatic group was 58 $\pm$ 16% with half the patients having a regurgitant fraction of > 60%. Although the mean value in the asymptomatic group did not differ appreciably (49 $\pm$ 13%), less than one fifth had a regurgitant fraction of > 60%.

In 8 asymptomatic and 4 symptomatic patients, the angiographic regurgitant fraction was compared to that measured using the electromagnetic flowmeter technique, with a good correlation (r = 0.85 in the asymptomatic and r = 0.82 in the symptomatic patients evaluated). These results again confirm that the patients evaluated in this study had a significant degree of aortic regurgitation.

VIII.3.0 EARLY POSTOPERATIVE EVALUATION:

The prognostic value of the pre-operative non-invasive evaluation of LV size, wall stress, systolic function and preserved exercise capacity is well accepted. Numerous echocardiographic variables have been cited as important prognostic indicators, with a pre-operative LV DES > 55mm (Grossman 1977, Bonow 1980, Cunha 1980, Henry 1980), LV DED > 80mm (Gaasch 1978, Clark 1980, Henry 1980, Stone 1984), fractional shortening < 29%, R/Th ratio > 4 (Gaasch

1978, Osbakken 1981, Kumpuris 1982) all being associated with an adverse prognosis. In addition, persistent postoperative LV dilatation with a DED > 70mm is a poor prognostic indicator (Gaasch 1978, Clark 1980, Henry 1980). It has been shown that the reduction in end-diastolic dimension (DED) occurs early, i.e. between 2 weeks and 2 months postoperatively (Venco 1976, Gaasch 1978, Schuler 1979, Henry 1980), with little further change at later evaluation. This decrease in end-diastolic dimension may be predicted by the pre-operative LV DES and fractional shortening (Clarke 1980, Henry 1980, Kumpuris 1982, Stone 1984). However, a recent long-term study (Fioretti 1985) has shown that a decrease in LV size continues beyond the first postoperative year and that the persistence of moderate LV dilatation after surgery does not indicate a poor clinical prognosis. This observation confirms the earlier work of Toussaint (1981). Importantly they also found that pre-operative M-mode echocardiographic variables were poor predictors of the clinical outcome and the regression of LV size. Fractional shortening (%FS) is generally not calculated postoperatively because of the invariable occurrence of paradoxical septal motion. This is thought to be a motion artefact caused by exaggerated systolic anteromedial translation of the entire frame of reference (Kerber 1982, Waggoner 1982, Force 1983).

Although systolic dysfunction (%FS or LVEF) at rest is widely reported as a sensitive predictor of ultimate outcome (Cunha 1980, Henry 1980, Forman 1981, Greves 1981), it is not specific, with improvement and even normalisation of LV systolic function frequently occurring despite severe pre-operative depression (Kennedy 1977, Gaasch 1978, Borer 1979, Schuler 1979, Schwarz 1979, Bonow 1980, Clark 1980, Ross 1981). In addition, the abrupt and

profound changes in loading conditions caused by aortic valve replacment, make the evaluation of LV systolic function particularly difficult in the early postoperative period.

Following surgical correction of chronic AR substantial changes in LV volume, mass and systolic performance are well described and are a function of the pre-operative severity and time (Gaasch 1978, Schuler 1979, Henry 1980, Carroll 1982, Kumpuris 1982, Carroll 1983, Fioretti 1985). Despite the controversy regarding the time course of postoperative changes in LV dimensions (Tousaint 1981, Kumpuris 1982, Gaasch 1983), both angiographic EDV (Kennedy 1977, Panteley 1978, Schwarz 1979, Clark 1980) and echocardiographic DED (Gaasch 1978, Schuler 1979, Henry 1980) have been used to show that most patients achieve a normal or near-normal end-diastolic volume following aortic valve replacement. In general it would appear those patients who normalise their EDV do so within the first 7 to 10 days after surgery. In patients with persistent LV dilatation, some show progressive chamber enlargement while others show no change or a modest decrease in heart size. The identification of this subset in the early postoperative period is thought to be important because aggressive medical therapy should be implemented in an attempt to reduce the high risk of congestive heart failure and early mortality.

In contrast to the postoperative changes in LV volume, the regression of left ventricular hypertrophy (LVH) is variable and may never be complete (Kennedy 1977, Gaasch 1978, Panteley 1978, Schuler 1979, Schwarz 1979, Clark 1980, Henry 1980). The factors responsible for incomplete regression of LVH following technically successful aortic valve replacement are not well defined. The

extent of myocardial fibrosis (Schwarz 1978), associated systemic hypertension, patient-prosthesis mismatch (Rahimtoola 1978), and perhaps genetic or other undefined factors may all be important. Regression of LVH is likely to be associated with a decrease in LV diastolic chamber stiffness, a major determinant of LV end-diastolic pressure. This could account for a gradual late improvement in congestive symptoms over and above that related to the early reduction in LV volume.

A normalisation or near-normalisation of LV end-diastolic pressure (LVEDP) commonly occurs following aortic valve replacement, even in patients with preoperative LV failure (Gault 1970, Kennedy 1977, Panteley 1978, Borer 1979, Schwarz 1979, Clark 1980, Henry 1980). The mechanisms are incompletely understood but a decrease in regurgitant volume is almost certainly the major factor and a change in LV diastolic compliance has been suggested by Gault (1970). A later study by Schwarz (1978) concluded that the LV "stiffness constant" did not change after aortic valve replacement but this study had several methodologic flaws, the most important of which was the timing of the assessment. Because LV mass is not stable in the early postoperative period, studies which aim to evaluate the physical properties of the LV in diastole should not be performed before 6 months. Although the above studies report a normalisation of LVEDP at rest, Lee et al (1971) have reported an abnormal elevation in LVEDP during exercise in several patients following aortic replacement (AVR). They postulated that this was due to persistent postoperative LV hypertrophy associated with a resultant decrease in diastolic compliance.

There are in general only modest changes in resting LVEF at 6

months after surgical correction of severe aortic regurgitation, with pre-operative values ranging from normal to severely depressed (Kennedy 1977, Panteley 1978, Borer 1979, Schuler 1979, Schwarz 1979, Clark 1980, Henry 1980). Although the time course of change in postoperative resting LVEF has not been defined, there is reason to believe that early postoperative studies might not reflect the eventual improvement. In a study by Boucher (1982), it was found that LVEF dropped significantly from 55 $\pm$ 12 to 40 $\pm$ 14% early postoperatively, associated with a marked decrease in EDV. They concluded that this early reduction was predominantly the result of altered loading conditions rather than improved contractile function. Most patients with normal pre-operative values remain unchanged, in contrast to patients with LV dysfunction in whom 25-50% can expect an increase in resting LVEF (Clark 1980, Henry 1980). Borer et al (1979) showed that despite a slight increase in resting LVEF following AVR, the response to exercise remained abnormal in most patients. As previously discussed, the LVEF is determined by a complex interplay between preload, afterload and the contractile state of the LV. In those patients with a postoperative decrease in EDV and some regression of LVH, it is likely that an increase in LVEF is due to a combination of a reduction in systolic wall stress (afterload) and/or an increased contractile state. Thus at optimal preload, a postoperative decrease in LVEF is likely to be related to excessive afterload and/or depressed LV contraction.

The early postoperative evaluation of my group of patients was thus designed to help examine the time course of change in both the anatomical and functional status of the left ventricle following successful AVR for chronic severe aortic regurgitation.

Although there was a significant reduction in LV end-diastolic dimension from 74 ± 11 to 58 ± 13mm ($p < 0.05$), only 38% (6 of 16 patients) normalised their DED early postoperatively. This is sharp contrast to the early reports quoted above where early normalisation was the rule. In addition, it should be appreciated that 4 of the 5 patients with marked LV dilatation pre-operatively, had significant residual LV dilatation postoperatively, with a LVDED > 70mm.

Although changes in end-systolic dimension (DES) are variable in the early postoperative period, there was a slight overall decrease in my study. More importantly however, is the observation that two-thirds (66%) of the patients with a pre-operative LVDES > 55mm, increased this dimension in the early postoperative period.

Only minor changes in cross-sectional area (CSA) were noted at 10 days postoperatively, which is in agreement with previous reports. One of the proposed mechanisms includes postoperative oedema of the posterior LV wall, and although apparent in some individual patients in my study, as a group posterior wall thickness remained unchanged. This probably reflects the fact that the regression of LV hypertrophy is a slow, time-dependent process.

Although paradoxical septal motion precluded the calculation of echocardiographic fractional shortening postoperatively, and appreciating the significant effect of changes in loading conditions on radionuclide determined LVEF, early postoperative LVEF was nevertheless measured. There was a uniform drop in early postoperative LVEF, confirming the results of Boucher et al (1981), with follow up data at 6 months (vide infra) showing that this merely reflected altered loading conditions rather than reduced LV

contractility.

Thus, in summary, my data confirms that in patients with moderate LV dilatation there is a uniform decrease in echocardiographic DED, although early normalisation only occurred in about one-third of my patients, possibly related to the degree of pre-operative LV dilatation. In addition it would appear that patients with marked pre-operative LV dilatation run a major risk of significant, persistent postoperative dilatation and a poor surgical result. The slow regression of LV hypertrophy is also confirmed and finally it would appear that the early assessment of LV systolic function can be obtained using the radionuclide LVEF, but has little relevance to the ultimate 6 month outcome.

VIII.4.0 SIX MONTH POSTOPERATIVE ASSESSMENT:

As previously discussed, the postoperative changes in LV volume, mass and contractile function are generally stabilised by 6 months (Gaasch 1978, Schuler 1979, Henry 1980, Carroll 1982, Kumpuris 1982), but further improvement has recently been reported up to 27 months postoperatively (Toussaint 1981, Fioretti 1985).

In general, it is reported that end-diastolic dimension normalises, and does so early. This is however contrary to my experience. Although regression of LV hypertrophy is usually incomplete, it is nevertheless associated with normalisation or near normalisation of resting LVEDP, sometimes despite pre-operative LV failure. Resting LVEF as a rule remains unchanged. However it has been reported that on exercise, LVEDP may rise, and the LV functional response remains abnormal in most patients. Nevertheless, the resting changes in mass and volume result in an overall improvement

in congestive symptoms following successful AVR for chronic severe AR.

VIII.4.1 Improved Functional Status:

My results are in agreement with previous reports (Kennedy 1977, Panteley 1978, Schwarz 1978) of an improvement in functional status, with 84% of my patients becoming asymptomatic and the majority of the rest improving by at least 1 functional class. It is thus encouraging to report that there appears to be little doubt that the quality of life can be appreciably improved by AVR in severe symptomatic AR.

VIII.4.2 Reduction in LV Voltage on Electrocardiogram:

Several previous studies have shown that the electrocardiographic (ECG) evidence for LVH is significantly decreased in approximately 75% of patients following successful AVR, with normalisation of voltage in about half of these (Schwarz 1978, Carroll 1980, Henry 1980). Despite only providing a semiquantitative measure of LV mass, it is a simple and inexpensive method of evaluating regression of myocardial hypertrophy, with most of the ECG voltage changes also occurring within 6 months of valve replacement surgery. In agreement with the above experience, a significant decrease in LV voltage occurred in 87% of my patients, but with normalisation in only one quarter. In this subset, the degree of pre-operative LV hypertrophy did not appear predictive, except to say that none had a modest degree (< 60mm) of LV hypertrophy on their electrocardiogram.

VIII.4.3 Decrease in Radiographic Cardio-Thoracic Ratio(CTR):

The importance of a postoperative decrease in heart size was emphasised in a report on the long-term results of AVR by Hirshfeld

et al(1974). Using the chest X-ray, they found that 85% of the patients with a postoperative reduction in heart size survived beyond 6 years compared to a 43% survival rate in those with an unchanged or increase in heart size. In my study, 89% of the patients had a reduction in CTR with approximately half this group having a normal heart size at the 6 month assessment. Thus my work confirms a reduction in CTR in the vast majority of patients following AVR for chronic severe aortic regurgitation, and it would appear that radiographic normalisation of heart size is common.

VIII.4.4 Postoperative Changes in LV Dimensions:

Although it appears to be generally accepted that changes in LV DED occur within 7 to 10 days following successful AVR (Hirschfeld 1974, Gaasch 1978, Henry 1980), more recent studies with bigger patient groups, have shown continued reduction in LV size after the first 8 months following valve replacement (Toussaint 1981, Fioretti 1985).

My series is in agreement with the more recent work, showing an overall reduction in LV DED by 42% at 6 months, but importantly, 40% of this overall decrease occurred relatively late, i.e. between the 10 day and 6 month assessment. Thus, although 38% of the group had normalised their DED early postoperatively, 72% had a normal LV DED at 6 months, confirming the overall impression that most patients achieve a normal or near-normal end-diastolic volume following AVR.

Although marked LV dilatation is uncommon in most reported series, including my own (22% had a DED > 80mm), three quarters (75%) had persistent postoperative dilatation with a mean LV DED of 68 $\pm$ 4mm. Although the prognostic significance cannot be assessed from my

the reported literature (Gaasch 1978, Schuler 1979, Carroll 1981, Carroll 1982). Forty four percent (44%) of my patients normalised their LV mass, 23% near-normalised (CSA < 24.0cm^2) and only one third of the group had significant persistent LVH. The mean pre-operative CSA for this subset was significantly higher (36.1 ± 5.5 versus 28.5 ± 10.1cm^2, p <0.01), refuting an earlier claim in a study on hypertension-induced LVH (Rowland 1982) that the greater the LV mass before treatment, the more marked the regression of the hypertrophy. However, this difference may be due to the different inciting stimuli and type of LV hypertrophy (Grossman 1980). Half the patients who normalised their LV mass postoperatively had severe pre-operative hypertrophy. Nevertheless, the numbers are small and one would be reluctant to postulate that the degree of pre-operative LVH may be predictive of postoperative regression.

When stratified into normal postoperative CSA (subset 1, n = 8) and persistent postoperative LVH (subset 2, n = 6), certain important differences were apparent (see Appendix VI). The degree of pre-operative LV dilatation was slightly higher in subset 2 (DED 76 ± 10 versus 69 ± 9mm, p = NS) and includes 3 of the 4 patients with marked LV dilatation. Although normalisation of pre-operative EDV was the rule in subset 1 patients (75%), persistent LV dilatation occurred in half the subset 2 patients. However, the degree of pre- and postoperative afterload stress was similar in the two groups, suggesting that the degree of LVH was appropriate for the chamber size and the maintenance of a normal systolic wall stress (Gaasch 1979, Panidis 1984).

Although pre-operative resting PCWP was significantly lower in the subset 1 patients (12 ± 4 versus 18 ± 4mmHg, p <0.01), the degree

of LV hypertrophy did not appear to significantly influence the postoperative, supine resting or peak exercise PCWP. Postoperatively there were similar incremental improvements in both resting and exercise radionuclide determined ejection fraction in both subsets. However, there was a slight (p = NS) but definite reduction in peak exercise PCWP in the subset with a normal postoperative LV mass which was significantly lower than the exercise value in the subset with persistent LV hypertrophy.

The most striking differences were in the resting and exercise peak and average diatolic filling rates. In the subset who normalised their LV mass postoperatively, incremental improvements ranged from 48% for resting average diastolic filling rate (p = NS) to 103% for exercise ADFR (p <0.01) and from 61% for resting peak filling rate (p <0.05) to 85% for exercise PFR (p <0.01). Importantly, these values were at similar heart rates (Bianco 1985) and thus appear to reflect a marked improvement and normalisation of diastolic function both at rest and on exercise in this subset of patients. This was also associated with an appreciably lower exercise PCWP and a higher LVEF in this group, highlighting the importance of diastolic relaxation and filling to adequate systolic function (Bonow 1981, Polak 1982, Bahler 1983, Bianco 1985). The exact implictions of this marked improvement in diastolic function on the long-term results of patients undergoing AVR for symptomatic severe AR remain to be determined.

VIII.4.6 LV Function at Rest and during Supine Bicycle Exercise after AVR in Patients with Chronic AR:

A major concern in chronic AR has been the development of irreversible myocardial dysfunction with late death from congestive heart failure despite technically successful AVR. For example, 78%

of late postoperative deaths from 1972 to 1978 in the National Institutes of Health study (Bonow 1982) were related to chronic congestive heart failure. As a result, several prognostic indicators relating to LV dimensions and systolic function have been proposed to aid in the appropriate timing of surgery and the identification of high-risk patients with a poor prognosis (Copeland 1977, Fischl 1977, Cunha 1980, Forman 1980, Henry 1980, Greves 1981, Gaasch 1983).

Using the rationale that a decrease in LVEF on exercise may represent an intermediate point between normal function and LV dysfunction at rest (Borer 1978), a pre-operative fall in LVEF on exercise has been suggested as a predictor of a high-risk group of patients who may have subsequent deterioration in myocardial function after AVR (Borer 1978, Borer 1979, Bonow 1982). However, during exercise there is a complex interplay of changes in preload, afterload and contractility, all of which may singly or in combination, influence the ejection fraction response to exercise, particularly in patients with chronic AR. Thus it is difficult, if not impossible, to differentiate changes in loading conditions from myocardial degenerative changes. There is increasing evidence that exercise-induced LV dysfunction in symptomatic patients is often reversible after surgery (Bonow 1983, Bonow 1984), and a recent study by Gee et al (1985) with a 30 month follow up period found no prognostic significance of exercise-induced LV dysfunction in chronic AR.

Most studies addressing changes in resting and exercise haemodynamics following AVR for chronic severe AR report an approximately 20% incidence of abnormal findings at re-evaluation

(Bristow 1964, Beck 1966, Lewis 1966, Ross 1966, Bjork 1967, Hultgren 1969). Despite intense interest in diastolic function particularly in patients with ischaemic heart disease, (Bonow 1981, Mancini 1983, Poliner 1984), hypertension (Inouye 1984, Fouad 1984, Smith 1985) and congestive heart failure (Monrad 1984), few reports address the problem in chronic volume overload (Eichhorn 1982) and to my knowledge there are no reports in patients following successful AVR.

Apart from the fact that LV dysfunction appears to be reversible, it has become appreciated that preserved exercise capacity (Bonow 1980) and the duration of pre-operative LV dysfunction (Bonow 1984) are important determinants of reversibility. However, a few recent reports suggest that improved operative techniques in the current surgical era rather than pre-operative LV function determines the postoperative result (Fioretti 1983, Daniel 1985, Fioretti 1985).

The good degree of haemodynamic improvement observed in the present study is in accord with the observations of other workers (Bristow 1964, Beck 1966, Ross 1966, Bjork 1967, Hultgren 1969). Exercise capacity improved by at least one exercise level in the majority of patients (2/3) and represents a 40% overall improvement in exercise duration. Normalisation of resting cardiac index occurred in 4 out of 5 patients with a depressed pre-operative value, and although resting PCWP remained abnormal in nearly one third of cases (32%), this represents a significant drop from the pre-operative assessment where 53% of patients had an abnormal resting LV filling pressure. However, in contrast to some previous reports, exercise PCWP remained markedly abnormal, with normalisation occurring in only 2 patients (12.5%). Obvious causes of residual cardiac

dysfunction after valve replacement surgery, including prosthesis insufficiency (Petersen 1967), pre-existing coronary artery disease (Linhart 1968) and persistent postoperative LV dilatation (Braun 1973) were not operative in this study. Although an increase in LVEDP on exercise in general reflects an increase in LV end-diastolic volume (Ross 1966), it has been postulated that this may be magnified by an increase in LV stiffness (Braunwald 1963). From my study it will be noted that at similar resting and peak exercise heart rates, both peak and average diastolic filling rates improved significantly with near-normalisation in the subset with regression of LV hypertrophy. Associated improvements included peak exercise PCWP, which was appreciably lower than in the group with residual LVH (25 $\pm$ 10 versus 35 $\pm$ 8mmHg, p = NS), and also peak exercise LVEF. Thus, although regression of LV hypertrophy is associated with improved diastolic filling and an appreciable reduction in exercise PCWP, normalisation is uncommon and this may reflect the preload dependance of this chronic severely volume overloaded LV following AVR.

Another important finding is that resting LVEF increased significantly with normalisation in 78% of those patients with abnormal pre-operative values. This finding is contrary to earlier reports from our own (Forman 1980) and other institutions (Cohn 1974, Fischl 1977, Greves 1981) citing a depressed pre-operative resing LVEF as a poor prognostic indicator. In agreement with the recent literature (Bonow 1982, Bonow 1983, Bonow 1984, Gee 1985), exercise LVEF increased appreciably from 45 $\pm$ 15 to 66 $\pm$ 19%, with normalisation in three-quarters of cases. In addition, the level of pre-operative exercise LVEF does not appear to be predictive, as 3 out of 5 patients in the subgroup with an exercise value of < 35%

normalised postoperatively.

Coincident with an improvement in clinical status and echocardiographic measures of LV mass and size, there is an improvement in exercise capacity, resting haemodynamics and radionuclide determined systolic and diastolic function. Significant improvements occurred in exercise systolic and diastolic function, but in contrast, persistent and marked elevation in exercise PCWP was noted. Markedly improved relaxation precludes the incrimination of abnormal diastolic stiffness as the operative mechanism and this must reflect significant LV dilatation on exercise. Thus it would appear that the previously chronic volume-overloaded LV of aortic regurgitation is critically preload dependent (Rankin 1975) in maintaining a normal resting and peak exercise (supine) LVEF following AVR.

Postoperatively the majority of these patients were limited by leg fatigue and not by shortness of breath as they were preoperatively, and improved diastolic relaxation may thus play a pivotal role in this late improvement in congestive symptoms on exercise.

VIII.4.7 LV Function at Equivalent Workloads During Supine Bicycle Exercise after AVR for Chronic Aortic Regurgitation:

Despite many reports on the postoperative evaluation of patients following aortic valve replacement for chronic AR, numerous factors make this comparison extremely difficult. Aortic valve replacement results in an abrupt change in preload due to the cessation of regurgitation, and is reflected by an appreciable decrease in early postoperative DED (Gaasch 1978, Schuler 1979, Henry 1980, Carroll 1982, Kumpuris 1982). Apart from the change in loading conditions,

prosthetic aortic valves are mildly stenotic, thus substituting mild pressure overload for severe volume overload. In addition, the exercise capacity is generally improved, thus a comparison of results at peak exercise in fact reflects changes at different external workloads.

In an attempt to minimise this latter variable, we evaluated LV function at equivalent workloads during supine bicycle exercise after AVR. Both haemodynamic and radionuclide variables showed little change between equivalent workload and peak supine exercise and thus this form of analysis appears to add little to the overall assessment of these patients. The importance of this, however, is that it is not necessary to exercise these patients to exhaustion.

VIII.4.8 LV Function at Rest and during Erect Bicycle Exercise after AVR in Patients with Chronic AR:

Contrary to earlier reports (Crawford 1979, Poliner 1980, Thadani 1981, Shen 1985), I have shown that there appears to be very little influence of posture on the exercise response of the left ventricle in patients with chronic severe aortic regurgitation. As a result, erect exercise, which more closely simulates normal daily activity, is recommended as the posture of choice for exercise evaluation. In an attempt to justify its use in the postoperative assessment of these patients, this posture was also used at the 6 month evaluation in my study. However, it should be noted that the sample size is much smaller (n = 9), because the tilting facility was not available pre-operatively in the other cases.

The pleasing haemodynamic improvement noted during supine bicycle exercise was mirrored in the erect posture. Resting cardiac index likewise normalised in 5 out of 6 patients with PCWP remaining

unchanged. Exercise heart rate was similar in the two postures but systolic BP significantly lower in the upright posture. The mean exercise PCWP also remained significantly abnormal, but normalisation occurred in a bigger percentage of patients (43% versus 12.5%).

Once again there was a marked increase in resting LVEF, with normalisation in 80% of those patients with reduced pre-operative values. Overall resting LVEF was higher in the erect posture (71 $\pm$ 17 versus 63 $\pm$ 14%) which is contrary to the effect of posture on LVEF in normal subjects where resting values are similar in both postures (Poliner 1980).

During erect exercise, LVEF increased significantly with normalisation of abnormal pre-operative values in a slightly higher percentage during this posture (83% versus 75%). Again, the level of pre-operative exercise LVEF did not appear predictive, with two-thirds of patients with marked reduction in pre-operative exercise LVEF (<35%) normalising postoperatively.

As occurred during the supine posture, a striking improvement in diastolic function occurred with normalisation of resting and near-normalisation of peak exercise PFR and ADFR.

Thus the overall improvements in haemodynamics and radionuclide-derived measures of systolic and diastolic function were similar during the two postures and amplifies our recommendation that the erect posture be the body position of choice in the exercise evaluation of these patients.

VIII.4.9 The Use of Isometric Handgrip in the Postoperative Evaluation of Chronic AR:

Despite some of the previously mentioned theoretical advantages of using isometric handgrip exercise as a means of LV stress, it has again been shown to be of no benefit in the postoperative evaluation of patients with chronic AR. This part of the study therefore reinforces our recommendation that this form of exercise has no role in the pre- or postoperative assessment of the effects of chronic volume overload due to aortic regurgitation on the structure and function of the left ventricle.

VIII.5.0 SEQUENTIAL ASSESSMENT:

Against the background of the common indications for valve replacement surgery (Rahimtoola 1977), increasing attention is being given to the role of early valve replacement in asymptomatic or minimally symptomatic patients with chronic severe aortic regurgitation (Kirklin 1973, Isom 1974, Smith 1976), particularly when associated with LV dysfunction (Henry 1980, Turina 1984). The rationale for early operation is the prevention of deteriorating myocardial function (Kouchoukos 1976).

However, more recently the excellent prognosis with conservative therapy in the subset of asymptomatic patients with chronic severe aortic regurgitation and normal LV function has been reported (Bonow 1983). The issue has been further complicated by the fact that most of the well known non-invasively determined prognostic indicators have at one time or another been shown to be of limited value (Linhart 1975), including an echocardiographic LV DES > 55mm and more recently the LV ejection fraction response to exercise (Gee 1985).

Nevertheless, there remains the worrying clinical problem of a group of patients who develop LV dysfunction prior to the onset of symptoms. The natural history study of Bonow et al (1983) showed that once LV dysfunction developed, symptoms were likely to develop within a short time (months). My own experience forms the subject of this last part of the discussion.

VIII.5.1 Clinical Status:

Functional status, the degree of LV hypertrophy on electrocardiogram and the cardio-thoracic ratio remained essentially unchanged over the 6 to 12 month follow-up period despite nearly half (12/26) of the patients having an LV DED of > 70mm and 4 out of 26 having a LV DES > 50mm. It would thus appear that on clinical grounds an annual assessment in asymptomatic patients with chronic severe aortic regurgitation seems adequate.

VIII.5.2 Serial Echocardiographic Dimensions:

Appreciating the limitations of the M-mode echocardiogram (Linhart 1975, Johnson 1976, Bhatt 1978, Abdulla 1980), the mean LV DED remained unchanged at 6 months, with only a small number (12%) showing progressive dilatation during this period. Two of the three cases had progressed into the range (> 70mm) predictive of the development of symptoms or LV dysfunction.

In the one patient where 12 month follow up was available, no further increase in DED occurred. None of the other echocardiographic measurements, namely, DES or fractional shortening or systolic wall stress were predictive of this change in diastolic dimension. In only one patient did progressive dilatation first occur at the 12 month assessment. Thus, in

summary, in an asymptomatic group of patients with chronic severe AR, LV diastolic size appeared to be relatively stable over a short term (12 month) assessment period, with progressive LV dilatation only occurring in a small minority of cases.

Similarly, end-systolic dimension (DES) remained stable over the first 6 month assessment period, but there was a progressive increase in DES in nearly half (4/9) the patients at the 12 month evaluation. The LV DES was > 50mm in 75% of these cases, and thus predictive of those patients who may increase their end-systolic dimension at serial assessment. The increase in DES was often associated with a fall in fractional shortening. Two of the three patients with a LV DES > 55mm at the 12 month assessment remained asymptomatic, although one (A.C) became symptomatic at 18 months and subsequently underwent successful aortic valve replacement.

VIII.5.3 Serial Echocardiographic Systolic Function and Wall Stress:

Fractional shortening (%FS) as a measure of systolic function remained stable over the 12 month sequential assessment period, although in 3 patients (12%) there was a progressive fall in FS to within the abnormal range at 12 months. All three were associated with a LV DES > 5.5cm.

Importantly, two of the patients who demonstrated an obvious fall in %FS at 6 months had no change in resting LVEF assessed by equilibrium radionuclide angiocardiography. It would thus be reasonable to recommend that a deterioration in echocardiographic systolic function be substantiated by another non-invasive measure in the serial assessment of asymptomatic severe AR.

Despite an overall unchanged systolic wall stress at 6 months, an

appreciable number of patients (38%) had a moderate increase in wall stress (411 ± 72 to 518 ± 73mmHg) due to progressive LV dilatation in some patients. Thus it would appear that inadequate hypertrophy is the operative mechanism in most cases where there is a progressive increase in systolic wall stress. When stratified on LV functional reserve (vide infra), the afterload in the subgroup with a normal functional reserve was significantly lower than in the group with a fall in exercise LVEF.

VIII.5.4 Serial Changes in Supine Resting Haemodynamics and Radionuclide Data:

In agreement with previous haemodynamic studies and the known pathophysiologic changes in chronic volume overload (Braunwald 1969, Lewis 1970, Judge 1971, Vatner 1976, Boucher 1983), resting heart rate and systolic BP remained essentially unchanged but there was a slight and progressive increase in LV end-diastolic pressure (PCWP) and an increase in echocardiographic LV end-diastolic dimension. In addition, a small progressive reduction in resting cardiac index was noted.

When stratified according to LV functional reserve, only minor changes were apparent, with a progressive increase in PCWP and decrease in cardiac index in both subsets. However, cardiac index remained within the normal range in the subgroup 1A patients despite a significant number of them developing an abnormal resting PCWP, signifying less severe LV dysfunction (Braunwald 1969).

Although systolic function as determined by radionuclide LVEF remained unchanged, with time there was a progressive fall in both peak and average diastolic filling rates in the subgroup 1B patients, and this impairment of diastolic function (increased

diastolic stiffness) may thus be a marker for an abnormal functional reserve in asymptomatic patients with chronic severe aortic regurgitation.

VIII.5.5 Serial Changes in Supine Exercise Haemodynamics and Radionuclide Data:

Exercise capacity was variable, although one-third of the group with a normal LVEF response and half the patients with an abnormal LV functional reserve increased their capacity by 1 exercise level (150k-p.m./min). This may be due to a training effect (Froelicher 1983), but more likely reflects familiarisation with the exercise protocol.

As occurred at rest, with time there was a progressive rise in PCW pressure on exercise, with a bigger percentage of patients developing abnormal exercise wedge pressures but maintaining the same cardiac output. This pattern of a progressive increase in PCWP only to be followed at a later stage by a fall in cardiac output has been well described (Braunwald 1969) and in haemodynamic terms represents an intermediate phase between normality and overt, severe LV dysfunction.

When divided according to LV functional reserve, patients with a fall in exercise LVEF demonstrated a higher systolic BP and PCWP i.e. afterload and in addition had significantly lower peak and average diastolic filling rates. Thus although the degree of afterload stress appears to significantly influence the LVEF response to exercise, abnormalities of diastolic filling appear to play a contributory role, with abnormal diastolic stiffness at rest being an early marker as suggested in the above discussion.

With time, one-third of patients with a normal functional reserve

developed a fall in LVEF on exercise. In one patient this was associated with an appreciable change in diastolic filling. A small minority (18%) of the subgroup 1B patients normalised their functional reserve without an apparent reason, doing so at 6 months in all cases. Thus, in some asymptomatic patients there appears to be a variable LVEF response to exercise.

Thus it would appear that in the sequential assessment of patients with asymptomatic severe AR there is a gradation of haemodynamic changes, starting with a progressive rise in both exercise and resting PCWP, and in patients with an abnormal LV functional reserve, associated with a reduction in resting cardiac index. In addition, a progressive increase in the number of patients with an abnormal LV functional reserve, was also noted.

This study thus confirms the observation by Borer et al (1979) that an abnormal LV functional reserve is common in asymptomatic patients with chronic severe AR and in addition shows that there is a progressive increase in the number of patients with this abnormality. Apart from excessive afterload being an important pathogenetic mechanism, confirming the work of Lewis (1982) and Greenberg (1985), it would appear that increased diastolic stiffness plays a contributory role in this response to exercise.

VIII.5.6 Serial Changes in Erect Resting Haemodynamics and Radionuclide Data :

In contrast to the progressive abnormalities in PCWP in both subsets and the reduction in resting cardiac index in subset 1B patients in the supine posture, no such changes were evident in the erect posture. Although this is in agreement with the recent observation by Shen et al (1985), I don't agree with their

recommendation that the supine position thus be the posture of choice for evaluation of these patients, as most of the other haemodynamic and radionuclide changes are similar (vide infra) and more importantly the majority of these abnormalities are fully reversible after aortic valve replacement.

In the erect posture, resting LVEF remained essentially unchanged over the 12 month follow up period, although one-third of patients (similar to the supine evaluation) with a normal functional reserve had a progressive fall in resting LVEF, however remaining within the normal limits. This drop in LVEF was associated with a significant decrease in diastolic filling rates and once again serves to highlight the importance of systolic-diastolic interaction (Bonow 1981, Polak 1982, Bahler 1983).

VIII.5.7 Serial Changes in Erect Exercise Haemodynamics and Radionuclide Data:

The serial exercise haemodynamic changes were similar during this posture, with a progressive rise and a greater percentage of patients (particularly subset 1) developing an abnormal PCWP on exercise but maintaining the same cardiac output.

As seen during supine bicycle exercise, exercise capacity improved in a similar number of subgroup 1A patients but in a much lower percentage (21% versus 50%) of subset 1B patients. Exercise LVEF remained unchanged although significantly lower in group 1B patients at 6 months. It is again evident that intersubgroup and intrasubgroup variation (6 months and 12 month assessments) in LV functional reserve correlates significantly with changes in diastolic filling. Changes in subset status were less frequent during this posture.

VIII.6.0 CONCLUSIONS:

In the overall analysis of this study I believe that a number of important conclusions can be drawn, some of which differ from previously published work. The explanation probably lies in the fact that this thesis must be seen in the South African context where severe valvular heart disease is a disease of the young. These conclusions will be numerically listed and include:-

1. The clinical features, including the electrocardiogram and chest X-ray, and degree of LV dilatation measured echocardiographically were similar in the two groups of patients studied. However, twice the number of symptomatic patients had marked LV dilatation (DED > 80mm). Thus clinical evaluation and echocardiography did not help differentiate the symptomatic from asymptomatic groups.

2. In both groups exercise posture was not important in the stratification of patients on the basis of the LV ejection fraction response to exercise. A similar percentage of patients had an abnormal LV functional reserve in both the supine and erect postures. Upright exercise is more physiological and therefore the posture of choice in the exercise evaluation of patients with chronic severe aortic regurgitation.

3. The haemodynamic profiles at rest and during peak exercise during both body positions are in agreement with previous reports. In the supine posture it is important to note that resting PCWP was abnormal in 50% of the asymptomatic group and abnormal in all of this group on exercise. Although resting

values were lower in the erect posture, similar peak exercise values were recorded. The ability to tolerate an extremely high exercise PCWP (range 30 - 50mmHg in the symptomatic group) appears to be a major compensatory mechanism in patients with chronic severe AR.

4. This study confirms that a drop in LVEF on exercise is common in patients with chronic severe AR, occurring in 81% of the symptomatic group and in approximately 50% of the asymptomatic patients. The resting value did not appear to be predictive, with a normal or equivocal exercise response occurring over a wide range of resting ejection fractions.

   The exercise LVEF correlated poorly with other measured variables (haemodynamic and radionuclide) and thus its usefulness in the management of these patients is questionable. This is not surprising given the known limitations of this dimensionless measure of LV function.

5. Although resting and exercise diastolic filling patterns (both peak and average diastolic filling rates) measured non-invasively were significantly abnormal in both groups of patients, marked improvement with near-normalisation occurred postoperatively. This was associated with a lower PCWP and higher LVEF both at rest and on exercise, highlighting the important contribution of diastolic relaxation and filling to adequate systolic function.

6. An abnormal functional reserve and elevation of PCWP occurred early during graded, supine, syptom-limited bicycle exercise and was generally maximal at level 2 or 3 of exercise. This

was followed by a plateau phase. Low level exercise is thus adequate to stratify patients, accepting the fact that exercise capacity has been demonstrated to be an independent prognostic factor.

7. Isometric exercise appears to be a poor form of stress in patients with chronic severe aortic regurgitation and is not recommended as an alternative to dynamic bicycle exercise.

8. The early postoperative assessment confirmed a uniform decrease in LVDED in the patients with moderate LV dilatation, but contrary to most reports, early normalisation occurred in only one third of the patients. In addition, patients with marked pre-operative dilatation run a major risk of persistent postoperative LV enlargement; my study confirms that regression of LVH is a slow process following aortic valve replacement.

9. The sequential evaluation of the asymptomatic patients showed a gradation in haemodynamic changes which was similar during both supine and upright exercise. There was also a progressive increase in the number of patients with an abnormal LV functional reserve and, although an increase in afterload appears to be the dominant mechanism, increased diastolic stiffness may play a contributory role. It is also important to note that some patients showed a variable LVEF response to exercise.

10. Findings at the six month postoperative assessment form the last conclusion and in summary serves to re-affirm our present practice at this institution of only recommending aortic valve replacement in symptomatic patients with AR.

(a) Postoperatively there was a marked improvement in symptomatic status and thus quality of life with 84% of the group becoming asymptomatic.

(b) Contrary to previous reports, normalisation of EDV following AVR can be a late phenomenon, occurring between two weeks and six months in about half the patients following valve replacement.

(c) A pre-operative DES > 55mm was found not to be a poor predictor of postoperative outcome with resting haemodynamics and LV functional reserve normalising in most cases.

(d) LV mass normalised or near normalised in the majority of cases undergoing AVR (77%). This observation is different to the reported literature.

(e) Exercise capacity improved by at least one exercise level in most cases.

(f) Despite normalisation of echocardiographic dimensions and resting LVEF, PCWP remained abnormal (> 15mmHg) at rest in one third of the patients. On exercise PCWP was markedly abnormal in 87.5% of the study group. This finding has not been appreciated in the past and although LVH regressed and diastolic filling improved in some cases, this finding may reflect the preload dependence of the chronically volume overloaded left ventricle.

(g) Both resting and peak exercise LVEF normalised in $\pm$ 75% of cases. This could not be predicted by the level of pre-operative exercise LVEF and thus serves to confirm a recent report that a drop in LVEF on exercise does not appear to be of prognostic significance.

(h) Finally, the influence of posture was again demonstrated

APPENDIX I:

BLOOD LABELLING

The patient's blood was labelled using the Brookhaven National Laboratory (BNL) Red Cell Kit for preparing Technetium-99m labelled red blood cells.

Four millilitres(4ml) of the patients blood was withdrawn into a heparinised 5ml syringe and this sample was then transfered to the 10ml capacity BNL vacutainer reagent tube containing 2.0 micrograms of tin, 3.67 milligrams of sodium citrate and 5.50 milligrams of dextrose. The blood containing BNL tube was then gently mixed for 5 minutes at room temperature to dissolve the freeze-dried solids in the blood.

Six millilitres(6ml) of sterile normal saline was then added to the tube to dilute any plasma trapped in the cell sediment, thus minimising the depression of red blood cell labelling yield. The tube was gently inverted 6-8 times to ensure adequate mixing. It was then centrifuged upside down for 5 minutes at 2900 revolutions per minute to separate the red blood cells: the tube was maintained in the inverted position to avoid disturbing the packed red cells. Using a sterile 20 gauge needle, approximately 1.2ml of packed red cells were removed and added to 30mCi(1110 megaBequerels) of Technetium-99m, in a volume of 1 to 3ml in a sterile pharmaceutical vile. The Technetium-red blood cell mixture was then incubated for 10 minutes at room temperature with gentle mixing. Labelling now being complete, the mixture was drawn into a sterile syringe and injected into the patient.

APPENDIX II:

LEFT VENTRICULAR EJECTION FRACTION NORMAL VALUES VARIATION, VALIDATION, REPRODUCIBILITY.

The following are the resting normal values for the Groote Schuur Hospital Cardiac Clinic/Department of Nuclear Medicine Laboratories.

A. NORMAL VALUES.

Forty four(44) subjects without clinical, chest X-ray or electrocardiographic evidence of cardiac disease were studied. Subjects included normal volunteers and patients with malignant disease being screened prior to therapy with the cardio-toxic agent Adriamycin. The mean left ventricular ejection fraction was 65% (S.D.$\pm$8%). We have accepted 65 $\pm$ 2 S.D. as normal i.e. 49-81%.

B. CORRELATION WITH CONTRAST ANGIOGRAPHY.

In 36 patients who had contrast right anterior oblique left ventriculography in the course of routine investigation and during the same admission had Multigated Equilibrium Blood Pool Scanning performed, the results of left ventricular ejection fraction by the two techniques were compared. Contrast left ventricular ejection fraction was calculated from the end-diastolic and end-systolic frames of the contrast left ventricular angiogram using the area-length method. Patients were unselected and included patients with regional left ventricular wall motion abnormalities and valvular heart disease. The correlation was good (R = 0.891).

C. INTER-OBSERVER VARIATION.

Eighty seven(87) studies performed on 39 patients were analysed by two different operators. The operators were unaware of results

obtained previously. There was a good correlation between the results obtained by the two operators (R = 0.978).

D. INTRA-OBSERVER VARIATION.

One hundred(100) studies performed on 42 patients were analysed on two separate occasions, more than 10 days apart by the same operator. The operator was unaware, at the time of the second analysis, of the initial results. There was a good correlation between the results obtained on the two analyses (R = 0.995).

E. REPRODUCIBILITY.

Fifty five(55) patients were studied with Multigated Equilibrium Blood Pool Scanning on two occasions. No interventions had been performed and there was no clinical, electrocardiographic or chest X-ray evidence of any change in their cardiac condition. The left ventricular ejection fractions were calculated without knowledge of the previous results. A good correlation was obtained (R = .975).

APPENDIX III:

ECHOCARDIOGRAPHIC MEASUREMENTS IN PATIENTS WITH AORTIC REGURGITATION

	NORMAL	CHRONIC AORTIC REGURGITATION		
		Compensated	Borderline	Decompensated
LV DEDI (cm/m2 BSA)	<3.4	<3.7	3.7 - 4.0	>4.0
LV DESI (cm/m2 BSA)	<2.3	<2.5	2.5 - 2.6	>2.6
LV FS (%)	>29	>29	25 - 29	<25
R/Th	<3.7	<3.8	3.8 - 4.0	>4.0
SWS mmHg (P.R/Th ed)	<450	<550	550 - 600	>600

APPENDIX IV:

ECHOCARDIOGRAPHIC RESULTS STRATIFIED ON LV FUNCTIONAL RESERVE: (Symptomatic Group)

GROUP 1A(n = 6)

	DEDI	DESI	FS	R/Th	SWS	CSA
*N.L.	4.7	3.5	24	3.7	592	26
*R.L.	2.7	1.4	48	2.9	269	26
*S.M.	4.1	2.4	40	3.1	465	23
*J.N.	4.3	2.9	32	3.4	482	20
*N.P.	4.4	3.1	29	2.2	330	38
*MvB.	3.2	2.4	25	3.1	465	23
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MEAN	3.9	2.6	33	3.1	434	26
±SD	0.8	0.7	9	0.5	21	6

GROUP 1B(n = 21)

M.A.	3.8	2.5	33	2.5	589	29
F.A.	5.1	3.3	35	2.5	456	43
R.A.	4.5	3.3	28	3.8	608	27
M.B.	4.9	3.9	21	4.4	1004	37
B.B.	5.3	3.2	40	3.5	588	36
R.C.	4.2	2.8	34	4.2	651	30
D.D.	4.0	2.6	36	2.2	331	25
MdV.	4.7	3.0	37	2.2	306	43
E.G.	5.1	3.3	35	3.5	560	30
K.G.	3.1	2.0	33	1.9	300	38
M.H.	4.0	2.8	30	2.9	401	48
B.H.	3.9	2.9	25	3.2	475	33
E.J.	3.9	2.6	34	2.7	542	29
J.L.	5.3	4.1	22	3.3	430	41
M.L.	4.0	3.4	15	4.3	595	19
H.M.	3.8	2.3	38	2.3	439	30
H.M.	4.6	3.3	28	3.0	450	32
M.N.	4.3	2.8	35	2.8	443	35
E.N.	3.9	2.7	32	2.7	382	26
P.P.	3.4	1.9	44	3.6	499	16
EvH	4.0	2.7	34	3.9	663	28
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MEAN	4.3	2.9	32	3.1	510	32
±SD	0.6	0.5	6	0.7	156	6

APPENDIX V:

ECHOCARDIOGRAPHIC RESULTS STRATIFIED ON LV FUNCTIONAL RESERVE (Asymptomatic Group)

GROUP 2A(n=13)

	DEDI	DESI	FS	R/Th	SWS	CSA
*S.A.	4.2	2.8	33	3.2	473	23
*M.B.	4.2	2.7	36	4.8	670	16
*S.C.	3.5	2.3	36	3.0	354	22
*A.C.	5.5	3.6	34	2.9	409	36
*P.J.	4.5	3.0	33	3.0	420	26
*J.J.	4.2	3.0	27	2.2	396	38
*S.M.	3.3	2.2	34	2.5	369	27
*F.N.	4.3	3.2	25	2.9	401	26
*N.O.	3.5	2.1	40	2.6	418	33
*J.P.	3.6	2.2	40	2.7	460	29
*C.V.	3.5	2.2	36	2.8	330	20
*D.V.	3.3	2.2	33	2.5	305	28
*A.W.	3.5	2.4	31	2.6	416	20
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MEAN	3.9	2.6	34	2.9	417	26
±SD	0.6	0.5	4	0.6	90	6

GROUP 2B(n=15)

L.A.	4.6	3.1	32	3.0	473	31
S.A.	4.5	3.1	32	4.8	950	21
G.D.	4.3	2.9	33	3.0	480	32
D.D.	3.9	2.6	34	2.8	477	35
H.H.	4.7	3.4	27	2.9	433	36
K.K.	4.5	3.1	30	3.3	491	29
P.M.	5.5	3.4	38	3.8	760	27
M.P.	4.1	3.0	26	2.3	369	30
I.R.	4.8	3.2	33	2.8	482	47
S.R.	4.0	2.5	37	2.5	375	27
W.S.	3.7	2.2	40	2.3	341	21
T.S.	4.3	2.6	39	3.5	490	30
A.T.	4.7	3.3	30	3.0	420	32
VdS.	4.5	2.9	34	3.4	547	36
L.V.	4.9	3.3	34	3.3	600	35
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MEAN	4.5	3.0	33	3.1	513	31
±SD	0.4	0.4	4	0.6	158	6

APPENDIX VI:

PRE- AND POSTOPERATIVE ECHOCARDIOGRAPHIC, HAEMODYNAMIC AND RADIONUCLIDE VARIABLES IN PATIENTS WITH NORMAL AND ABNORMAL LV MASS FOLLOWING AVR: (Mean ± S.D.)

	NORMAL CSA (n = 8)		ABNORMAL CSA (n = 6)	
	PRE-OP	POSTOP	PRE-OP	POSTOP
CSA	28.5 ± 10.1	16.4 ± 2.7	36.1 ± 5.5	29.1 ± 2.3
EDV	6.9 ± 0.9	4.8 ± 2.2	7.6 ± 1.0	5.6 ± 1.4
SWS	486 ± 95	292 ± 48	452 ± 139	310 ± 146
FS	28 ± 11	32 ± 6	33 ± 6	32 ± 16
HR R	90 ± 16	80 ± 29	86 ± 11	75 ± 12
PCWP R	12 ± 4	13 ± 4	18 ± 4	16 ± 5
EFR	50 ± 16	63 ± 12	54 ± 13	64 ± 22
PFR R	1.97± 1.11	3.17± 1.36	2.27± 0.88	2.33± 0.83
ADFR R	0.99± 0.53	1.47± 0.69	1.15± 0.49	1.05± 0.37
HR EX	162 ± 12	162 ± 19	134 ± 13	156 ± 16
PCWP EX	31 ± 11	25 ± 10	31 ± 13	35 ± 8
EF EX	44 ± 20	67 ± 16	41 ± 11	59 ± 25
PFR EX	3.04± 1.30	5.62± 1.22	2.92± 1.03	3.13± 1.56
ADFR EX	1.51± 0.96	3.06 ± 0.09	1.18± 0.51	1.21± 0.59

R = Rest

Ex = Peak Exercise

APPENDIX VII:

SUPINE EXERCISE AT EQUIVALENT EXTERNAL WORKLOADS:

(LEVEL 1: 150k-p.m./min)

SYMPTOMATIC GROUP (n = 31)									ASYMPTOMATIC GROUP (n = 28)								
PT	HR	SBP	CI	FFI	W	EF	PFR	ADFR	PT	HR	SBP	CI	FFI	W	EF	PFR	ADFR
MA	130	200	4.4	34	34	54	2.48	-	SA	132	160	6.7	51	13	63	4.00	2.05
FA	110	230	4.8	44	40	60	-	-	LA	120	210	6.3	53	24	54	2.67	1.34
RA	107	200	6.2	58	15	57	2.86	1.58	SA	100	200	5.7	57	18	56	1.98	1.13
MB	100	230	4.3	43	45	39	1.55	0.75	MB	110	180	5.6	51	25	66	2.63	1.82
BB	116	210	5.9	51	32	54	2.72	1.17	SC	100	160	4.8	48	17	66	2.78	1.50
RC	95	170	3.3	35	23	38	1.31	0.62	AC	100	170	5.4	38	15	55	3.99	2.00
DD	115	200	6.7	58	29	69	4.43	2.16	GD	120	190	6.0	50	27	53	2.07	1.26
MdV	120	200	5.1	43	52	56	3.81	1.77	DD	90	190	4.7	52	25	57	2.97	1.46
EG	125	190	4.6	36	25	32	-	-	HH	110	180	7.4	68	21	51	2.00	1.07
KG	130	220	4.8	36	33	49	3.56	1.77	PJ	110	150	5.0	45	15	51	3.52	1.74
MH	102	220	4.2	41	-	38	-	-	JJ	104	180	5.8	56	20	68	2.43	1.52
BH	116	200	-	-	-	38	2.67	0.89	KK	120	190	5.5	46	21	56	3.45	1.71
EJ	138	240	5.8	42	35	61	3.16	1.65	GM	100	170	5.5	55	15	61	2.61	1.43
JL	100	145	5.8	58	17	35	2.38	1.33	PM	85	200	5.5	65	17	58	-	-
NL	145	165	4.8	33	25	31	1.48	0.86	FN	160	200	6.2	38	30	40	3.23	1.64
RL	95	150	6.0	63	15	77	2.77	1.41	NO	90	180	5.1	57	11	65	2.47	1.53
ML	130	190	2.7	21	50	28	1.59	0.96	MP	168	190	6.4	38	30	67	4.98	2.13
SM	120	190	5.4	45	18	71	-	-	JP	80	190	5.4	68	18	66	1.89	1.18
HM	132	190	4.2	32	31	33	-	-	JR	112	215	4.3	39	24	53	3.15	1.56
NM	130	160	7.3	56	7	78	-	2.94	SR	110	180	4.9	44	43	57	3.55	1.48
HM	120	210	4.4	36	23	44	1.78	1.07	WS	108	170	4.0	37	15	59	3.21	1.85
MN	130	200	7.4	57	25	44	1.75	1.14	TS	110	170	5.4	49	32	39	2.13	0.91
EN	140	150	7.5	54	20	56	4.02	1.61	FT	114	150	6.1	53	27	51	2.17	1.36
JN	120	160	5.5	46	38	66	2.74	1.74	SvS	95	190	7.9	83	16	60	2.61	1.64
PN	96	170	6.1	63	14	56	3.09	1.77	LV	110	210	7.6	69	25	53	2.58	1.33
GN	110	160	7.9	72	14	60	3.11	1.60	CV	88	130	5.6	64	12	62	2.22	1.41
NP	120	140	6.1	51	23	46	1.47	0.57	DV	85	140	5.6	66	25	64	2.86	1.46
PP	100	160	5.2	52	29	60	3.07	1.81	AW	170	180	5.4	32	15	68	4.46	2.17
MvB	110	180	4.0	36	33	49	2.83	1.37									
EvH	100	180	-	-	-	49	2.26	1.28									
HW	110	190	5.7	52	21	56	3.23	1.74									
MEAN	117	187	5.4	46	27	51	2.64	1.42	MEAN	111	179	5.7	53	21	58	2.91	1.54
±SD	14	27	1.3	12	11	14	0.85	0.53	±SD	23	21	0.9	12	7	8	0.79	0.32

PT = patient initials
HR = heart rate
SBP = systolic blood pressure
CI = cardiac index
FFI = forward flow index
W = pulmonary capillary wedge pressure
EF = ejection fraction
PFR = peak filling rate
ADFR = average diastolic filling rate

APPENDIX VIII:

SUPINE EXERCISE AT EQUIVALENT EXTERNAL WORKLOADS:

(LEVEL 2: 300k-p.m./min)

SYMPTOMATIC GROUP (n=30)									ASYMPTOMATIC GROUP (n=28)								
PT	HR	SBP	CI	FFI	W	EF	PFR	ADFR	PT	HR	SBP	CI	FFI	W	EF	PFR	ADFR
MA	160	210	5.8	36	38	52	-	-	SA	154	180	7.2	47	11	60	2.46	1.14
FA	125	250	5.3	43	35	60	4.87	2.35	LA	135	210	8.4	62	22	54	4.02	1.82
RA	142	230	7.4	52	14	51	3.47	1.65	SA	110	210	7.0	63	16	56	2.76	1.60
MB	130	270	5.7	44	50	36	-	-	MB	118	185	6.7	56	22	65	2.89	1.82
BB	142	260	6.0	42	31	51	2.34	1.30	SC	122	170	5.6	46	15	75	3.68	1.92
RC	110	180	3.6	33	23	31	1.11	0.47	AC	130	190	7.0	39	15	58	5.24	2.77
DD	125	210	8.0	64	26	72	3.93	1.59	GD	128	190	6.2	48	20	51	2.67	1.65
MdV	140	220	6.6	47	55	52	3.82	1.91	DD	98	210	6.1	62	25	52	3.37	1.78
EG	142	220	4.8	34	28	28	2.35	0.89	HH	110	180	7.4	68	21	51	2.00	1.07
MH	110	220	4.3	39	-	35	2.49	1.02	PJ	128	165	6.6	52	18	45	4.62	1.72
BH	122	220	-	-	-	38	2.07	0.96	JJ	115	190	6.9	60	18	73	2.82	1.81
BJ	130	240	6.1	47	25	57	2.78	1.78	KK	140	220	6.7	48	25	53	3.72	1.82
JL	115	150	5.5	47	13	38	2.53	1.43	GM	110	180	6.0	54	16	64	2.96	1.90
NL	150	160	5.0	34	16	31	1.56	0.86	PM	100	200	7.0	70	18	57	1.89	1.07
RL	108	175	6.7	62	20	78	3.82	1.78	FN	168	210	7.2	43	30	40	3.62	1.59
ML	150	220	3.4	23	45	26	2.01	1.04	NO	100	190	5.8	58	9	65	2.66	1.76
SM	140	190	5.7	40	24	75	-	-	MP	188	210	8.5	45	30	68	4.21	2.02
HM	148	190	4.1	28	30	28	-	-	JP	90	190	5.9	65	19	69	2.18	1.49
NM	150	180	8.3	55	8	77	-	3.50	IR	126	220	5.1	41	25	50	3.01	1.45
HM	145	240	5.4	38	26	48	3.61	1.32	SR	124	190	6.3	51	33	58	3.87	1.72
MN	155	220	7.4	48	28	35	2.15	1.00	WS	126	180	5.2	41	16	60	-	-
EN	150	170	7.4	49	20	50	4.12	1.84	TS	120	190	5.9	49	25	37	2.16	0.91
JN	140	170	5.7	41	40	71	4.86	2.55	FT	130	170	6.8	52	28	44	1.90	1.24
PN	114	200	8.7	76	14	59	3.22	1.59	SvS	110	210	7.6	69	18	58	3.45	1.74
GN	130	180	9.0	70	15	58	4.88	2.33	LV	130	230	8.3	64	30	50	3.14	1.48
NP	150	160	8.4	56	37	46	4.07	1.62	CV	102	140	6.4	63	12	69	2.73	1.48
PP	110	180	5.8	53	28	61	4.02	2.21	DV	90	160	6.1	68	21	62	3.03	-
AW	185	200	5.4	29	14	68	5.01	2.79									
MvB	120	210	4.0	33	35	49	2.88	1.63									
EvH	120	210	-	-	-	48	1.44	0.74									
HW	125	210	6.8	55	20	56	3.33	1.61									
MEAN	133	205	6.1	46	28	50	3.11	1.58	MEAN	125	192	6.6	54	20	58	3.19	1.68
±SD	16	31	1.6	12	12	15	1.09	0.66	±SD	25	20	0.9	11	6	10	0.90	1.29

APPENDIX IX:

SUPINE EXERCISE AT EQUIVALENT EXTERNAL WORKLOADS:

(LEVEL 3: 450k-p.m./min)

	SYMPTOMATIC GROUP(n=22)									ASYMPTOMATIC GROUP(n=28)								
PT	HR	SBP	CI	FFI	W	EF	PFR	ADFR		PT	HR	SBP	CI	FFI	W	EF	PFR	ADFR
MA	170	230	6.2	36	38	52	3.06	1.54		SA	190	210	8.3	44	15	54	3.25	2.02
FA	150	300	6.6	44	40	54	4.91	2.04		LA	170	230	8.6	50	20	54	4.48	2.88
RA	167	240	9.7	58	16	50	3.14	1.41		SA	140	230	8.4	60	15	56	4.67	2.66
BB	158	270	6.9	44	32	49	2.42	1.42		MB	130	200	7.3	56	25	61	3.07	1.85
DD	145	220	9.1	63	26	66	-	-		SC	140	180	6.3	45	15	78	3.98	2.70
MH	124	250	4.9	39	-	32	2.14	0.89		AC	130	210	8.3	64	14	60	5.19	2.51
EJ	150	260	6.7	45	32	50	3.15	-		GD	155	200	6.8	44	34	43	-	-
JL	125	160	6.5	52	35	35	3.26	1.18		DD	98	230	8.2	84	25	58	3.77	2.14
NL	170	180	5.3	31	18	29	1.32	0.71		HH	140	230	8.6	61	17	55	3.08	1.84
RL	120	200	8.4	70	16	78	4.34	2.13		PJ	145	170	6.9	48	24	47	3.96	1.84
ML	160	240	4.5	28	38	24	2.58	1.12		JJ	130	195	8.5	65	18	66	2.84	1.42
SM	150	200	6.3	42	30	77	-	-		KK	160	250	7.5	47	23	55	4.75	2.11
NM	155	175	9.4	61	8	78	-	2.80		GM	125	200	7.7	61	15	69	4.77	1.82
HM	160	250	5.9	37	25	36	1.98	-		PM	130	220	8.8	49	20	50	3.07	1.29
MN	180	250	8.1	45	33	36	1.99	1.04		FN	170	210	7.3	43	25	46	4.05	1.48
EN	150	170	7.9	53	15	53	5.56	2.56		NO	112	190	6.6	59	8	62	2.91	1.85
JN	180	170	7.3	40	48	67	4.49	2.58		MP	180	210	8.3	46	25	65	3.54	1.49
PN	144	210	10.2	71	17	51	3.02	1.33		JP	104	210	7.5	72	15	66	2.54	1.63
GN	170	210	11.6	68	15	58	6.01	2.94		IR	148	240	5.9	40	31	46	3.97	1.95
PP	130	210	6.2	48	33	52	2.79	1.41		SR	140	220	7.0	50	30	50	3.68	1.62
EvH	130	210	-	-	-	43	2.45	1.37		WS	162	200	5.5	34	20	54	-	-
HW	140	240	8.5	61	20	55	3.35	2.00		TS	140	190	6.1	44	28	38	-	-
										FT	140	180	8.0	57	26	44	2.05	1.24
										SVS	130	230	10.4	80	19	58	4.97	2.12
										LV	160	260	10.5	66	37	44	3.52	1.92
										CV	115	160	7.9	69	13	68	3.18	1.84
										DV	100	160	6.5	65	18	64	2.84	1.69
										AW	198	210	6.9	35	15	83	6.33	3.36
MEAN	151	220	7.4	49	27	51	3.26	1.69		MEAN	142	208	7.7	55	21	57	3.78	1.97
±SD	18	36	1.8	13	11	15	1.26	0.68		±SD	25	25	1.2	13	7	11	0.97	0.51

APPENDIX X:

ABBREVIATIONS

ADFR	=	Average diastolic filling rate
AoP_s	=	Systolic aortic pressure
AoP_d	=	Diastolic aortic pressure
AR	=	Aortic Regurgitation
ATP	=	Adenosine triphosphate
ATPase	=	Adenosine triphosphatase
AVR	=	Aortic valve replacement
BNL	=	Brookhaven National Laboratories
BP	=	Blood pressure
BSA	=	Body surface area
CHF	=	Congestive heart failure
CI	=	Cardiac index
cm^2	=	Centimeter squared
cm/M^2	=	Centimeter per meter squared
CSA	=	Cross-sectional area
CTR	=	Cardio-thoracic ratio
^oC	=	Degree Centigrade
DED	=	Dimension at end-diastole
DEDI	=	Dimension at end-diastole indexed
DES	=	Dimension at end-systole
DESI	=	Dimension at end-systole indexed
ECG	=	Electrocardiogram
ed	=	End-diastole
EDP	=	End-diastolic pressure
EDV	=	End-diastolic volume
EDVI	=	End-diastolic volume indexed
EDV/sec	=	End-diastolic volume per second
EF	=	Ejection fraction
eg	=	Example
EOA	=	Effective orifice area
ERNA	=	Equilibrium radionuclide angiocardiography
ESV	=	End-systolic volume
ESVI	=	End-systolic volume indexed
EWL	=	Equivalent workload
Ex	=	Peak exercise
Ex.cap	=	Exercise capacity

F	=	French
FFI	=	Forward flow index
FS	=	Percentage fractional shortening
G	=	Gram
G/cm^3	=	Gram per centimeter cubed
Gr.	=	Group
Group 1A	=	Symptomatic patients with normal exercise LVEF
Group 1B	=	Symptomatic patients with abnormal exercise LVEF
Group 2A	=	Asymptomatic patients with normal exercise LVEF
Group 2B	=	Asymptomatic patients with abnormal exercise LVEF
h	=	Wall thickness
HR	=	Heart rate
Inf.	=	Infective
k-p.m./min	=	kilo-pond meters per minute
LAO	=	Left anterior oblique
L.E.M.	=	Low energy mobile
L/min	=	Litres per minute
$L/min/M^2$	=	Litres per minute per meter squared
LV	=	Left ventricular
LVDED	=	Left ventricular dimension at end-diastole
LVEDP	=	Left ventricular end-diastolic pressure
LVEDVI	=	Left ventricular end-diastolic volume indexed
LVEF	=	Left ventricular ejection fraction
LVESVI	=	Left ventricular end-systolic volume indexed
mB	=	Megabyte
mCi	=	Millicuries
ml	=	Milliliter
ml/b/min	=	Milliter per beat per minute
mm	=	Millimeter
mmHg	=	Millimeters of mercury
mm/sec	=	Millimeters per second
m.p.h.	=	Miles per hour
M.D.S.	=	Medical Data System
n	=	number of patients
NIH	=	National Institutes of Health
NS	=	Not significant
NYHA	=	New York Heart Association
P	=	Systolic blood pressure (cuff)
pCO_2	=	Partial pressure of carbon dioxide
PCW	=	Pulmonary capillary wedge
PCWP	=	Pulmonary capillary wedge pressure

P.Ex	=	Peak exercise
PFR	=	Peak filling rate (diastolic)
post	=	Postoperative
pre-	=	Pre-operative
PSG	=	Peak systolic gradient
PSP	=	Peak systolic pressure
PT	=	Patient initials
PWT	=	Posterior wall thickness
%	=	Percentage
R	=	Rest
r	=	Correlation coefficient
RF_A	=	Angiographic regurgitant fraction
RFF	=	Electromagnetic flowmeter regurgitant fraction
RNA	=	Ribonucleic acid
RPP	=	Rate pressure product
R/Th	=	Radius to wall thickness ratio
SBP	=	Systolic blood pressure
S.D.	=	Standard deviation
sec	=	Second
SVI	=	Stroke volume index
SWS	=	Systolic wall stress
Th	=	Posterior wall thickness
TPFR	=	Time to peak filling rate
µm	=	Micrometers
USCI	=	United States Catheter and Instrument Company
viz	=	Namely
vs	=	Versus
W	=	Pulmonary capillary wedge pressure
WS	=	Systolic wall stress

Please note that the Echocardiographic dimensions are expressed in either centimeters or millimeters.

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